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NASH'S
SURGICAL PHYSIOLOGY

THE NEW SECOND EDITION OF

NASH'S SURGICAL PHYSIOLOGY

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INTRODUCTION TO FIRST EDITION

The surgeon is often unaware of the large amount of physiological knowledge which he continually applies in his daily work. Nevertheless physiology is a constantly acting force guiding the work of the most avowedly practical surgeon. Though all aspects of surgery involve physiology in some degree, in certain of the newer developments of surgery physiology is actually the predominant consideration, operations being directed to the relief of functional rather than structural disorder.

The aim of surgery is to cure or relieve the patient. The aim of surgical progress is, in effect, to eliminate the need for surgery. No one will deny that physiology has been an indispensable instrument in bringing about a great many of the more recent advances in surgery, and many surgeons look upon this widening of the field of surgery as one of the desirable goals to be achieved by the cultivation of physiology. The benefits of surgery are undoubtedly being constantly extended to an ever greater number and variety of conditions. Yet, when one reflects upon the fact that in an ideal state of affairs there would be no surgery at all, it seems reasonable to look upon some of the present new extensions of surgery, however gratifying in themselves, as only temporary and partial benefits; still further progress in surgery, in physiology and in many other sciences will render them obsolete and unnecessary as new means of prevention or as effective non-surgical methods of treatment are discovered.

When the surgeon does not happen to know the physiological explanation of a clinical fact or group of facts he is sometimes inclined to improvise one, perhaps without the advantage of an adequate general knowledge of physiology. In some instances his hypotheses are not constructed with proper regard for well established physiological principles and cannot be harmonized with the latter. The result is needless confusion. When, as sometimes happens, an ill founded hypothesis is promulgated with a tone of assurance by an individual of great and perhaps well merited reputation as a clinical surgeon, many are misled, particularly among the younger surgeons, into mistaking unwarranted theory for established fact. The consequence is often a regrettable waste of energy in misguided thought and misdirected effort.

Surgery by its very nature inclines one to favor isolated facts of regional applicability, but the writer believes that a survey of the general

INTRODUCTION TO SECOND EDITION

JOSEPH NASH expressed the hope that his book, *Surgical Physiology*, would "be of help not only to the postgraduate student and the practicing surgeon, but also to the student and intern, in connection with their work in Surgery" His purpose was to present simply and briefly those aspects of physiology which are of especial importance to the surgeon The difficulties of sorting and selecting the material to be included in his book, *Surgical Physiology*, were, of course, appreciated by the author

It is obvious that the portions of physiology vital to surgery change from day to day and among surgeons, depending upon their field of activities Moreover, it is apparent that the authors and the readers of this book in many instances will neither have the capacity for nor interest in a complete treatise of physiology

In this new edition of *Nash's Surgical Physiology*, some of the original chapters are intact Others have been revised or completely replaced The revision has been a joint effort of members of the Department of Surgery and Dr Hugo V Rizzoli, of the Department of Neurological Surgery, the George Washington University School of Medicine

The editor desires to thank the various contributors for their efforts And particular gratitude is expressed to Miss Margaret M Hartnett, Secretary to the Department of Surgery, for her painstaking work in the preparation of the manuscripts

It is our sincere hope that the book as it now stands will be useful and serve, as nearly as possible, the purposes outlined by Joseph Nash before his tragic and untimely death during World War II

Brian Blades, M D

INTRODUCTION TO FIRST EDITION

The surgeon is often unaware of the large amount of physiological knowledge which he continually applies in his daily work Nevertheless physiology is a constantly acting force guiding the work of the most avowedly practical surgeon Though all aspects of surgery involve physiology in some degree in certain of the newer developments of surgery physiology is actually the predominant consideration operations being directed to the relief of functional rather than structural disorder

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Surgery by its very nature inclines one to favor isolated facts of regional applicability, but the writer believes that a survey of the general

functional plan of each system somewhat in "outline" form, even though lacking some details, supplies the most useful background for the interpretation of clinical phenomena Among the various systems of the body some are more "vital" than others, in the sense that suspension of their function is more rapidly fatal By this criterion, the circulation is the "most vital" system, since death results if the circulation is suspended for a number of seconds, respiration is the "next most vital" system, since death results if respiration is suspended for a number of minutes Some of the other systems of the body can remain out of function for days, weeks or months without fatal results

The circulation and respiration, being the two "most vital" systems, are of continued concern to the surgeon and are discussed first, even though operative procedures directed to these two systems are not exceptionally frequent The importance of the circulatory and respiratory systems to the anesthetist is obvious

The "general resistance" of the patient is often of concern to the surgeon, and a clear notion of the meaning of the term is desirable The term obviously refers to the efficiency with which the patient's various organs and systems function Hence, it is concerned to a considerable extent with physiology However, general resistance embraces much outside the usual limits of physiology In ordinary usage the term denotes the ability of the patient to withstand and recover from the deleterious effects of an operation or a disease On reflection it is apparent that "general" resistance does not exist as a separate and measurable entity, but rather consists of an immense number of *particular* factors, some known and some unknown, some measurable and others not measurable Some of the factors, such as blood pressure, pulse rate and vital capacity, have to do with physiology, but others, which are at times of greater clinical importance, belong to other sciences such as hematology, immunology, bacteriology, pathology and clinical medicine

In estimating the "general resistance" of an individual patient, as many factors as possible should be taken into account But discretion must be used in giving weight to the various factors, for this has to be done with reference to the particular strain or hazard to which the patient is exposed For example, the vital capacity is of great importance in a case in which an intrathoracic operation is contemplated but is of little significance in a minor operation on an extremity In connection with spinal anesthesia, the patient's blood pressure is of more importance than the red blood cell count In infections, the blood count is in general a more significant resistance factor than the blood pressure and the immunologic status of the patient is of more importance

than his muscular development In all cases even after every known factor has been taken into consideration there remain numerous unknown factors the combined influence of which can only be estimated on the basis of accumulated clinical data

Physiological answers to many surgical problems are yet to be found As surgeons we should not lose patience with or lose interest in physiology on that account Rather let us seek to discern clearly the present outer limits of certain knowledge however restricted they may be and to learn where the gaps are so that they may be filled

PREFACE TO FIRST EDITION

THE PURPOSE of this book is to present simply and briefly those aspects of physiology which are of especial importance in surgery Some branches of physiology which (at present) are chiefly of medical rather than surgical significance are omitted The choice of material is somewhat arbitrary, and in a few instances it may seem that topics of little use to the surgeon have been included These seemingly extraneous topics are included in the belief that they give promise of achieving greater application in surgery in the near future, or that surgery is likely to contribute to the solution of some of the physiological problems involved A special effort has been made to achieve clarity and conciseness, and to include the important recent contributions Though there is a temptation to digress upon discussions of surgical problems of a strictly clinical character, this has been avoided as far as possible as foreign to the purpose of the book

The scope of physiology is somewhat indefinite in the minds of both surgeons and physiologists It has certain traditional limits Many of the theoretical problems of surgery involve sciences other than physiology, such as physics, biochemistry, pathology, clinical pathology, bacteriology and immunology In connection with many operations, these other sciences are of greater importance than physiology, except with regard to the effects of the anesthetic agents employed Therefore, only a fraction of the "basic science" pertaining to surgery is comprehended under physiology Moreover, the material presented in this volume is not expected to fill the surgeon's needs for physiology perfectly and completely, rather it is intended to help and encourage the surgeon to make a more thorough study of this ("pre-clinical") science as specific problems arise in connection with his clinical work

Operative technique is only the apex of the great pyramid of surgical knowledge, it is the broad and heavy base that is most needed and most difficult to construct That leaders in the art of surgery consider a knowledge of physiology indispensable for the modern surgeon is evident from the fact that the American Board of Surgery, formed in 1937, and the other Boards of surgical specialties, require that candidates for certification by the boards give evidence of knowledge of those aspects of the science of physiology which have surgical applicability

It is hoped that this book will be of help not only to the post-graduate

student and the practicing surgeon but also to the student and interne in connection with their work in surgery

Articles and treatises on special subjects from which material has been obtained are cited in the list of references at the end of the book A conscientious effort has been made to give due credit in all cases Special indebtedness to the following larger works is acknowledged Davis' *Neurological Surgery* Gask and Ross' *Surgery of the Sympathetic Nervous System* White *Autonomic Nervous System* Kuntz's *Autonomic Nervous System* Peters *Body Water* Peters and Van Slyke *Quantitative Clinical Chemistry Interpretations* Wechsler's *Text Book of Clinical Neurology* Wiggers *Circulation in Health and Disease* and *Glandular Physiology and Therapy* a series of articles published in 1935 in the *Journal of the American Medical Association* under the auspices of the Council on Pharmacy and Chemistry of the American Medical Association and subsequently republished in book form To the last mentioned work I am indebted for much of the material in Section V Among the general texts which have been consulted may be mentioned Hewlett's *Pathological Physiology of Internal Diseases* McDowall's *Clinical Physiology* Rost's *Pathological Physiology of Surgical Diseases* and Wright's *Applied Physiology*

I am deeply indebted to Dr Robert W Clarke Instructor in Physiology at Yale University School of Medicine for valuable advice and assistance and for corrections and suggestions throughout the work To Dr Homer W Smith Professor of Physiology at New York University College of Medicine I am grateful for friendly guidance during my years as instructor in his department and for his generous encouragement in the present undertaking I wish to express my thanks to the following members of the faculty of New York University College of Medicine who were kind enough to go over sections of the manuscript and all of whom made valuable corrections and suggestions Dr R Keith Cannan Professor of Chemistry Dr Donal Sheehan, Professor of Anatomy Dr William Goldring Associate Professor of Medicine, and Dr Norman Jolliffe Associate Professor of Medicine I am indebted to Miss Mary Lorenc staff artist of the Departments of Anatomy and Surgery, for the preparation of the illustrations

This book has been developed on the basis of lectures given by the writer since 1930 as part of the Graduate Course in Surgery at New York University College of Medicine This Graduate Course in Surgery was originated in 1920 by Dr Arthur M Wright, Professor of Surgery at New York University College of Medicine and Director of the Third Surgical Division Bellevue Hospital, and has been con

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It is hoped that this book will be of help not only to the post graduate

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Joseph Nash

Fort Devens, Massachusetts

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NASH'S

SURGICAL PHYSIOLOGY

Chapter 1

GENERAL PHYSIOLOGY OF THE CIRCULATION

THE HEART AND GREAT VESSELS

OPERATIONS upon structures of the circulatory system or for the purpose of modifying the circulation have not always been as frequent as other surgical procedures In the last decade, however, surgical operations on the great vessels have become commonplace During the next few years it is hoped that open operations in the heart will become possible

Circulatory events often assume major importance in relation to all types of surgery, sometimes suddenly or unexpectedly In most of his work, however, the surgeon's chief concern with the circulatory system is that the circulation as a whole be adequate to carry the patient through the operation and its possible sequelae

The circulation of the blood is a strictly mechanical process, the primary essential for its adequate maintenance is an appropriate pressure of oxygenated blood Since all the factors which can influence the circulation of the blood have some relation to the maintenance of blood pressure, the general scheme of the circulatory system may be conveniently outlined by describing these various factors in relation to blood pressure regulation By "blood pressure" we mean the general level of the pressure within the arteries, i e the "mean arterial pressure," without special reference to systolic or diastolic pressure

The circulatory system consists of two separate circulations the pulmonary circulation and the systemic circulation (Figure 1) The pulmonary circulation is a low pressure system with a weaker pump, capable of standing stress less well than the systemic circulation pump The blood vessels in the pulmonary system are thinner walled than the systemic circulation vessels, for a lower head of pressure is maintained The normal pulmonary artery pressure is approximately thirty millimeters of mercury systolic and ten millimeters of mercury diastolic, as contrasted to one hundred and twenty millimeters of mercury systolic and eighty millimeters of mercury diastolic in the systemic circulation The blood received and put out by the pump in the pulmonary circulation is venous blood In contrast to this, the systemic circulation re-

some cases it is difficult or impossible (by present methods) to determine these remote factors, but an understanding of the mechanical features of the circulatory disturbance is always useful

In common clinical practice only the systemic circulation pressure can be measured The measurement of the pulmonary circulation blood pressure is usually estimated indirectly through changes in the size of the heart or pulmonary vessels seen in a roentgen ray film of the chest At times a cardiac catheter is passed into the right ventricle or pulmonary artery and direct pressure readings taken This is seldom done except when specific disease is suspected in the pulmonary circulation Normally the output of the left and right pumps is equal If at any time either of these pumps ejects more or less blood than the other pump for a protracted period marked changes such as peripheral venous congestions or pulmonary venous engorgement will result For the most part, in health, the pulmonary circulation is a passive circulation which follows passively the lead of the systemic circulation Thus adrenalin which raises the systemic blood pressure, will cause a rise in the blood pressure of the pulmonary circulation a short time after the response has started in the systemic circulation Further investigative work is to be done to evaluate mechanisms which can cause primary changes in the pulmonary circulation

THE HEART

Minute Output The only function of the heart is to develop pressure in the pulmonary and systemic circulations The heart is the primary source of all blood pressure—arterial, capillary and venous The important physiological consideration in regard to the heart is the *per minute heart output* also called the *minute volume*, which is the volume of blood injected into the aorta by the left ventricle during one minute Under basal conditions, per minute heart output is remarkably constant in any given individual, its value being proportional to the surface area of the body, as is the case with the metabolic rate The output can be measured most accurately by means of a cardiac catheter and by use of the Direct Fick method. Figure 2 (A and B) shows a chest film with various positions of the catheter When the catheter has been placed in the pulmonary artery, it is possible to withdraw a mixed venous sample of blood supposedly identical with the blood going to the lungs The oxygen content of this is determined If it were 70 per cent saturated and its capacity were normal, it would contain 14 0 cubic centimeters of oxygen per 100 cubic centimeters of blood Arterial blood can be aspirated from any artery by means of a

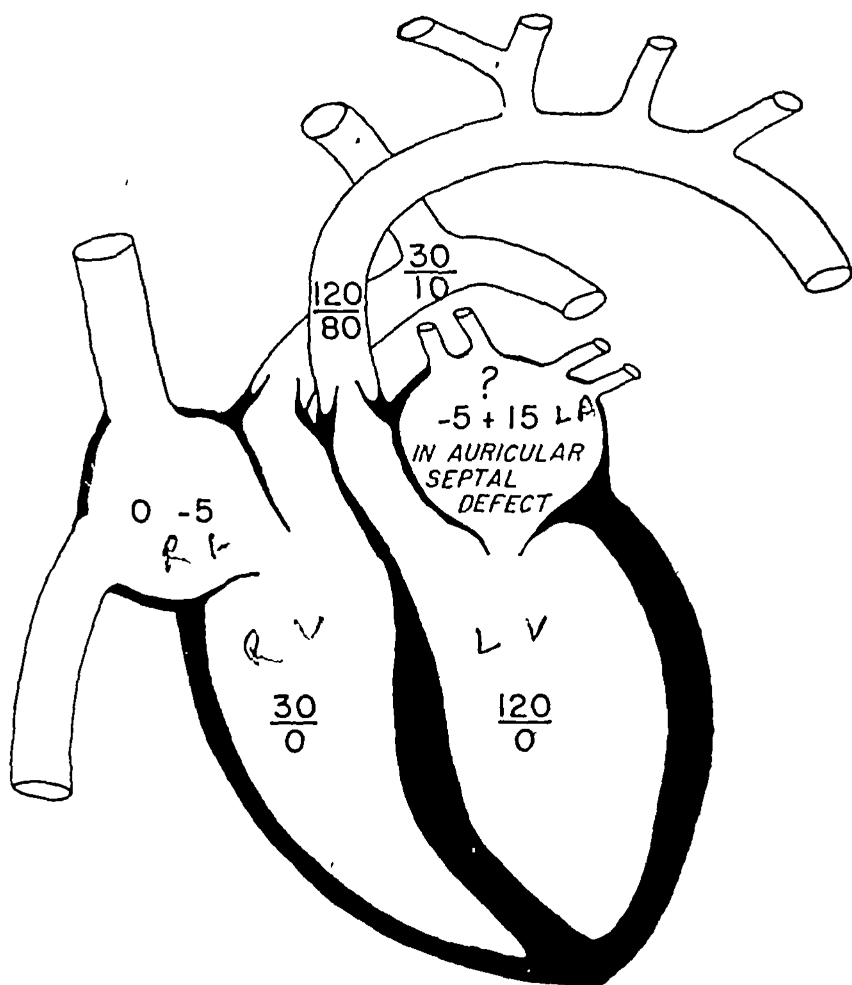


FIG 1 The diagram illustrates the pressures found in the chambers of the heart and the great vessels The pressures, expressed as millimeters of mercury, have been obtained in the intact human patient by means of the cardiac catheter technic These are only approximate figures The pressure in the pulmonary artery has been found to be 25/7

ceives oxygenated blood, and oxygenated blood is pumped outwards from it

Each of these separate circulatory systems proper consists of three parts the heart, the blood vessels and the blood These, the pump, the pipes and the fluid are the only structures which can have any direct part in maintaining pressure or in bringing about an alteration of pressure This simple fact is deserving of emphasis, for in a multitude of clinical conditions high or low blood pressure is a conspicuous feature demanding explanation One or more of the three elements named must be responsible for the altered pressure and the first requisite is to determine which of these elements is at fault Then the more remote factors which induced the change in these elements may be sought In

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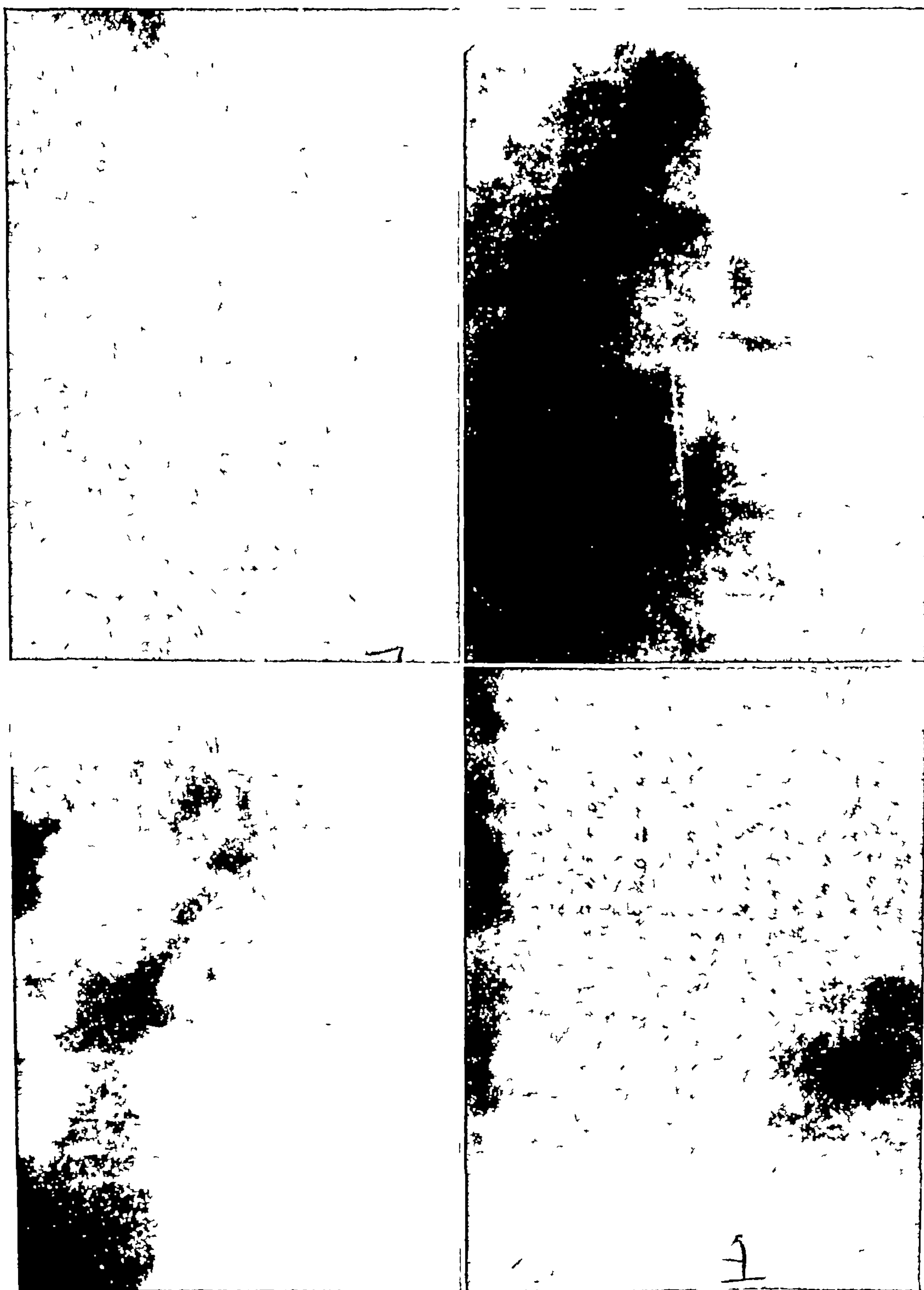


Fig 2(a)



FIG 2(b)

FIG 2 (a) These x rays demonstrate various positions of the cardiac catheter #7 catheter is the superior vena cava #6 catheter is in the right auricle #5 catheter is past the tricuspid valve #4 catheter is in the right ventricle (b) These x rays demonstrate various positions of the cardiac catheter #3 catheter is in the outflow tract of the right ventricle #2 catheter in the pulmonary artery and #1 catheter in the right pulmonary artery (Courtesy of Dr John Evans.)

needle or cannula simultaneously with the collection of the venous sample This is normally 95 per cent saturated which, in the instance above, would mean 19 0 cubic centimeters of oxygen per 100 cubic centimeters of blood Then the arterio-venous difference would be five cubic centimeters of oxygen per 100 cubic centimeters of blood The oxygen consumption is determined for the same period by a metabolism machine If the oxygen consumption were 225 cubic centimeters of oxygen per minute the cardiac output would be 4 5 liters per minute

The normal value for the cardiac output, measured by means of the cardiac catheter, averages about 3 1 liters per square meter of body surface This means the average male has a cardiac output of about 4 5 liters per minute while upright at rest and about 6 liters per minute while supine It is apparent then that the greater the heart output the higher will be the blood pressure Pipes and fluid remaining unchanged, the more the pumping the higher the arterial pressure The factors which determine the heart output (per minute) will be reviewed briefly

(1) Stroke Volume The volume of blood ejected each minute is the volume ejected by each heart beat (*stroke volume*) multiplied by the number of beats during the minute (*heart rate*) The stroke volume is determined largely by the amount of venous filling during diastole, i e, the more blood the heart contains at the end of a given diastole, the more it pumps out in the following systole This principle is not a self-evident one, as might seem to be the case It depends upon an inherent physiological property of heart muscle It is expressed in another way as Starling's *law of the heart,* which states that the force of contraction of the heart muscle increases in proportion to the distention of the heart, i e, to the initial length of the muscle fibers at the time they begin to contract This law is true to an optimum point (Figure 3)

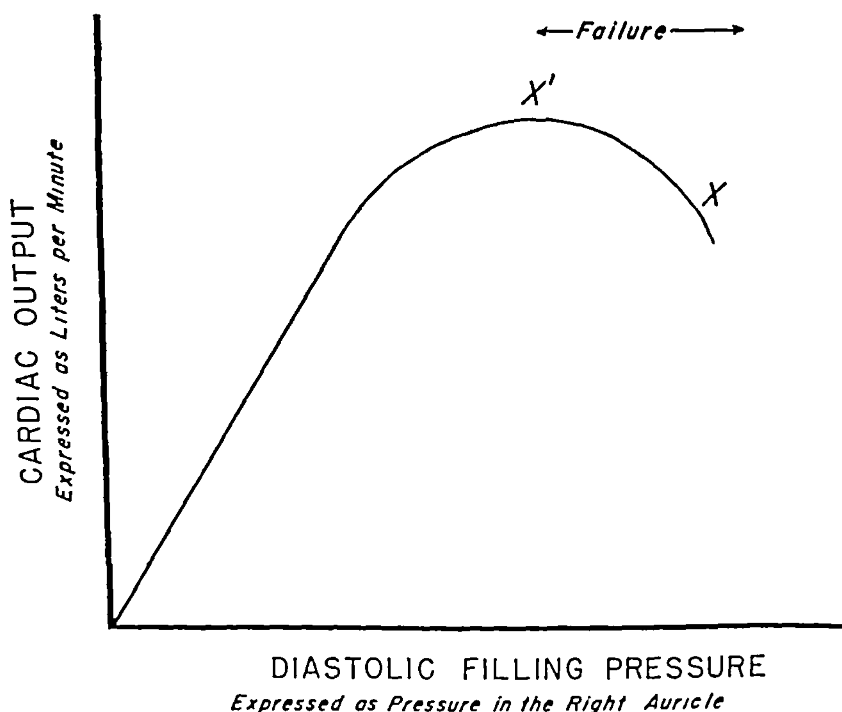


FIG 3 Diagrammatic representation of Starling's Law of the Heart Optimum output at X X[1] demonstrates "high output failure" where a further increase in diastolic filling has caused a fall in cardiac output

Beyond the optimum point any further increase in venous filling of the heart will be followed by a falling off of the force of contraction This means that, up to an optimum point, the greater the venous filling during a given diastole the more distended the heart is at the beginning of the next systole and the more forcibly it contracts on this larger amount of contained blood, therefore the greater is the stroke volume Other things being equal the greater the output per beat (stroke volume) the greater the output per minute (heart output) and the higher the blood pressure Conversely, the less the venous filling during diastole, the lower the blood pressure Various mechanisms which increase or decrease the venous inflow will be mentioned later

The concept of high and low output cardiac failure is evident in Figure 3 In mitral stenosis and in left ventricular failure due to long standing hypertension the patient may ultimately go into congestive failure Measurement of the cardiac output while the patient is in failure will reveal outputs below normal The lowest outputs found will usually occur in severe degrees of mitral stenosis This is failure with low cardiac output Conversely, in thyrotoxicosis or in severe pernicious anemia, the cardiac output will be markedly increased to two to three times normal values These patients may also go into congestive failure due to the inability of the heart to maintain or increase these high output figures Thus these patients will be in failure with high diastolic filling pressures and elevated cardiac outputs probably located in the vicinity of point X on the graph in Figure 3 This fact is important for surgeons to remember, e g patients with severe anemia who receive rapid transfusions may suddenly go into cardiac failure because the sudden increase in diastolic filling may cause a lowered cardiac output Thus, when possible, anemia should be corrected before surgery, and as a general rule blood should be replaced as it is lost

Diastolic filling may also be affected to some extent by pressure conditions on the aortic side of the heart and also on the pulmonary artery side of the heart In the presence of arterial hypertension the high pressure in the aorta for instance, tends to impede the emptying of the left ventricle and the latter may be pictured as emptying itself only partially at a particular beat, some blood remaining within its cavity Then during diastole the usual amount of blood enters and, together with the left-over from the preceding beat, distends the ventricle more than usual The contractility of the heart muscle is augmented by this overdistention in accordance with the law of the heart Therefore the succeeding systole is more powerful and the stroke volume is increased so that it is again at least equal to the value it had

before the hypertension interfered An instance of this simple mechanical regulation of the stroke volume is found in the hypertension associated with increased intracranial pressure In spite of the high aortic pressure opposing the heart in the slow heart rate, increased amplitude of contraction aids in maintaining adequate heart output (per minute)

In pulmonary embolism due to blood clots the pulmonary vascular system is obstructed partially or completely, depending upon the size of the clot If the clot be large, inadequate blood will reach the left ventricle Coronary artery blood flow and systemic blood flow will soon fall to dangerously low levels, and death will supervene If the degree of obstruction be less, the patient may survive In this situation the pressure in the pulmonary artery proximal to the obstruction will be elevated, the pressure in the right ventricle will also be raised and the pressure in the veins leading to the right heart will be above normal This acute cor pulmonale may also be detected by changes in the electrocardiogram produced by the increased work of the right ventricle and possibly aggravated by the lower coronary artery flow It is possible that the diastolic filling of this right ventricle may be so increased that the output of the right ventricle will diminish in accordance with Starling's law of the heart However, if the right ventricle output is any place to the left of X^1 in Figure 3, any maneuver which lowers the diastolic filling may cause a further reduction in the cardiac output, which could be disastrous

At times the ill effects of a pulmonary embolus seem out of proportion to the degree of obstruction produced in the pulmonary vascular system Experimentally, in anesthetized animals, 40-60 per cent of the main pulmonary arteries can be obstructed with no observed impairment It has been suggested that reflex spasm of the pulmonary vascular bed may be caused by obstruction of part of its bed Much discussion has taken place without settling the question From the author's unpublished data, it seems that the pulmonary vascular reflexes are important in pulmonary embolism

Heart Rate In a normal adult at rest the stroke volume is about 70 cubic centimeters During muscular exertion it may increase to about double this value The heart rate is the other of the two factors which determine heart output (minute volume) When increased activity of the body, whether due to exercise, toxemia, fever or any other cause, calls for an increased per minute volume of blood, the rate of the heart may rise from the average normal of 72 up to 150 or even 180 per minute Usually the increment in rate is proportionately somewhat greater than the increase in stroke volume Certainly it is the more

conspicuous change clinically for there are no simple means available by which alterations in stroke volume may be readily detected In athletically trained individuals the pulse rate increase in response to exercise is less marked than in the untrained, indicating a relatively greater adaptation by means of stroke volume increase and suggesting that the latter is the more efficient means of augmenting blood flow

Under some circumstances, heart rate may increase while stroke volume remains unchanged or even decreases The effect of the heart upon the blood pressure is always determined by the product of the two, i e, the heart output and cannot be estimated from either factor alone Of course, even if the combined effect of rate and stroke volume is known, this does not give any information as to the actual blood pressure level, since the latter is determined not only by the heart, but also by the other two "structures" of the circulatory system, namely, the blood vessels and the blood

Control of the Heart This may be taken to mean principally control of the rate The rate is the expression of the property of rhythmicity (automaticity) inherent in all parts of the heart muscle, but most highly developed in the specialized muscle cells which constitute the normal pacemaker This pacemaker in the right auricle can keep the heart beating rhythmically independent of all extracardiac factors, e g, in the excised heart, but in the body this inherent rhythm is always being modified A great number of physiological mechanisms are capable of influencing the rate of the heart Practically all of these can be included under one of the two headings chemical control and nervous control.

CHEMICAL CONTROL OF THE HEART AS AFFECTED BY CERTAIN SIMPLE IONS AND ALSO BY MORE COMPLEX SUBSTANCES, HORMONES, SECRETED BY THE ENDOCRINE GLANDS

The *sodium ion* in a certain concentration in the blood plasma is necessary for proper activity of all the properties of heart muscle This is believed to be due to some specific function of the sodium ion in maintaining the "physiological state" of the tissue, in addition to its large influence in preserving normal osmotic relations between the heart and the fluid medium in which it is bathed *Potassium ions* have an inhibitory effect upon the heart and are one of the normal factors which favor the relaxation phase of the heart cycle An excess of potassium causes the heart to cease beating in a state of extreme diastole ("potassium inhibition") *Calcium ions* promote contraction of the

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NERVOUS CONTROL OF THE HEART

① **The Vagus** Nervous control of the heart is effected through the vagus and sympathetic nerves The vagus may be considered the more important of the two It is active at all times, i e, it exerts a continuous restraining influence upon the heart, keeping it beating at a slower rate than would be the case if its intrinsic pacemaker (the sino auricular node) were unchecked This normal vagus tone is quite strong in that its removal leads to a marked increase in the heart rate which occurs very promptly Such removal or "inhibition" of the normal vagus tone is largely responsible for the tachycardia in nearly all clinical conditions associated with acceleration of the heart

Afferent Influences on the Vagus Center Viewing the vagus as the efferent limb of a reflex arc and the vagus center in the medulla as the center of the arc, what are the paths of the afferent influences which reach the center and by stimulating it cause the heart to beat slower, or by inhibiting it, cause the heart to beat faster? As a general answer to this question, it may be stated that all the potential afferent pathways capable of affecting the vagus center are *all the afferent nerve fibers in the body*

This concept is of fundamental importance in relation not only to the vagus control of the heart but also to all other nervous mechanisms for the control of viscera It means that all types of sensation from all parts of the body can affect the rate of the heart via the vagus center, though they may or may not do so according to circumstances All afferent nerve impulses, of whatever type, are conducted into some part or other of the central nervous system (spinal cord or brain), and once within it there is at least the possibility of a pathway to every center within the central nervous system Which centers will be affected by a given afferent impulse depends partly upon the anatomical arrangement of the fiber tracts, but to a greater extent upon the delicate grading of the resistances at various synapses within the central nervous system In other words, all afferent pathways are in structural connection with all efferent paths, either closely or remotely, since the former enter and the latter emerge from the central nervous system The actual flow of impulses from afferent to efferent paths is regulated by the enormously complex functional organization of the central nervous system Thus, hearing a sudden loud noise (eighth cranial nerve) or being immersed in cold water (cutaneous nerves) may lead to a change in pulse rate (vagus nerve) by this reflex mechanism But not every type and intensity of sensation or afferent impulse is equally potent in this regard and in order that the heart rate may not be incessantly interfered with

heart muscle, experimentally an excess of calcium ions causes a standstill of the heart in an extreme systole, a condition known as "calcium-rigor." In certain surgical conditions associated with disturbance of the concentration of the various ions in the blood, as in intestinal fistulae or pyloric obstruction, there is an appreciable deleterious effect upon the heart itself and an interference with these normal chemical regulators. Potassium ion in excess or potassium ion in deficiency apparently produces changes that can be detected in electrocardiographic tracings.

Carbon dioxide induces relaxation of the heart, probably not by a specific action, but by raising the hydrogen ion concentration. Overbreathing, which may occur during the induction period of anesthesia and perhaps in any condition associated with pain, tends to wash out carbon dioxide from the alveoli of the lungs and thus to reduce its concentration in the blood. Excessive artificial respiration has the same effect. It is possible that excessive loss of carbon dioxide may sometimes be a contributory cause of poor heart function in certain clinical conditions. Conversely, however, carbon dioxide retention occurs whenever ventilation is depressed and may occur during prolonged thoracic operations when the high partial pressure of carbon dioxide causes an extreme acidosis. This in turn may be responsible for some of the cardiac arrests that are seen clinically.

Adrenalin stimulates the heart, increasing both the rate and the force of contraction and so tends to raise the blood pressure. *Thyroxin* likewise increases the rate of the heart. These hormones act directly upon the heart itself and also affect it through the mediation of its autonomic nerve supply.

The hormone control of the heart generally comes into play slowly after an appreciable latent period, following the original stimulus initiating the cardiac response. Cardiac responses evoked by nervous influences, on the contrary, usually take place promptly, the latent period between the stimulus and the effect being short. Furthermore, the response by way of the nervous system is of relatively short duration which ceases when the stimulus ceases, whereas, effects produced by way of the hormones tend to lag, outlasting the stimulus for some time.

These differences between hormone control and nervous control are found in all the organs of the body which are subject to both types of control. It may be stated as a general rule that responses mediated through nerves occur promptly and are brief in duration, whereas those mediated through hormones begin after a latent period and last a considerable length of time.

NERVOUS CONTROL OF THE HEART

(1) **The Vagus** Nervous control of the heart is effected through the vagus and sympathetic nerves The vagus may be considered the more important of the two It is active at all times, i e it exerts a continuous restraining influence upon the heart, keeping it beating at a slower rate than would be the case if its intrinsic pacemaker (the sino-auricular node) were unchecked This normal vagus tone is quite strong in that its removal leads to a marked increase in the heart rate which occurs very promptly Such removal or 'inhibition' of the normal vagus tone is largely responsible for the tachycardia in nearly all clinical conditions associated with acceleration of the heart

Afferent Influences on the Vagus Center Viewing the vagus as the efferent limb of a reflex arc and the vagus center in the medulla as the center of the arc what are the paths of the afferent influences which reach the center and by stimulating it cause the heart to beat slower, or by inhibiting it, cause the heart to beat faster? As a general answer to this question, it may be stated that all the potential afferent pathways capable of affecting the vagus center are *all the afferent nerve fibers in the body*

This concept is of fundamental importance in relation not only to the vagus control of the heart but also to all other nervous mechanisms for the control of viscera It means that all types of sensation from all parts of the body can affect the rate of the heart via the vagus center, though they may or may not do so according to circumstances All afferent nerve impulses, of whatever type, are conducted into some part or other of the central nervous system (spinal cord or brain), and once within it there is at least the possibility of a pathway to every center within the central nervous system Which centers will be affected by a given afferent impulse depends partly upon the anatomical arrangement of the fiber tracts, but to a greater extent upon the delicate grading of the resistances at various synapses within the central nervous system In other words, all afferent pathways are in structural connection with all efferent paths, either closely or remotely, since the former enter and the latter emerge from the central nervous system The actual flow of impulses from afferent to efferent paths is regulated by the enormously complex functional organization of the central nervous system Thus, hearing a sudden loud noise (eighth cranial nerve) or being immersed in cold water (cutaneous nerves) may lead to a change in pulse rate (vagus nerve) by this reflex mechanism But not every type and intensity of sensation or afferent impulse is equally potent in this regard and in order that the heart rate may not be incessantly interfered with

by every chance afferent impulse, afferent impulses from certain particular regions are especially effective in influencing the heart rate, and predominate over the other afferent impulses

Bainbridge Reflex and Depressor Reflex It is not surprising that the most potent afferent impulses for controlling the heart arise in certain portions of the circulatory system itself, particularly those regions from which the heart receives and into which it discharges the blood The heart rate is thus largely regulated according to the factors of "supply and demand" On the venous or "supply" side of the heart the *Bainbridge reflex* causes acceleration of the heart when the venous inflow is so excessive that it overdistends the right auricle The sensory endings of this reflex arc are in the right auricle and nearby portions of the venae cavae and are stimulated by increased tension The afferent fibers run in the vagus trunk When there is overdistention of the auricle due to increased venous inflow, the resultant nerve impulses inhibit the vagus center so that the heart beats faster, thus tending to raise the heart output to balance the inflow

On the arterial side there is the so-called *depressor reflex* whose afferent fibers arise about the root and arch of the aorta and run to the medulla within the vagus nerve In some lower animals they constitute a separate nerve known as the depressor nerve The adequate stimulus for these fibers is tension within the aorta, the higher the tension the greater the stimulus When the aortic pressure is elevated it causes afferent impulses to ascend to and stimulate the vagus center, so that the heart beats more slowly, this decreased activity of the heart tends to reduce the blood pressure to its proper level The reverse occurs also, lowered aortic pressure giving rise to afferent nerve impulses (possibly in a different set of vagus fibers) which inhibit the vagus center and so accelerate the heart by diminishing the vagus tone

The Carotid Sinus· A similar depressor reflex, dependent chiefly upon the pressure within the carotid artery for its activity, has its afferent nerve endings in the carotid sinus, which is a specially innervated part of the arteries and surrounding tissues located at the bifurcation of the common carotid artery These structures consist of the origin of the internal and external carotid and occipital arteries, the carotid bulb (a bulbous dilation at the root of the internal carotid), and the carotid body located between the bifurcation of the arteries The afferent fibers reach the medulla via the glossopharyngeal and vagus nerves and the sympathetic trunk They are stimulated by high and low intracarotid pressure and slow or accelerate the heart by affecting the vagus center in just the same way as do the aortic depres-

sor fibers already described Above 200 and below 50 millimeters of mercury arterial pressure, reflex control of the circulation by means of the carotid sinus ceases These nerve endings are sensitive also to oxygen lack and to carbon dioxide excess, and aid in accelerating the heart when either of these conditions is present The carotid body which was formerly thought to be an endocrine organ, is almost certainly concerned in the reception of these chemical stimuli It has not been shown that any of the nerve fibers connected with it are efferent in function The afferent cardioaortic and carotid sinus nerve fibers described above have been aptly termed by Heymans the "moderator nerves"

(4) The higher centers of the brain itself may also be considered one of the special regions for initiating "afferent" impulses for cardiac control, for emotion may cause nerve impulses to descend to the medulla, where they are equivalent to afferent impulses in their ability to affect the vagus center so as to cause a change of heart rate Increased intracranial pressure is usually associated with slowing of the heart, brought about by overstimulation of the vagus center This stimulation has been attributed both to direct mechanical stimulation of the vagus center cells in the medulla by the pressure, and to ischemia of the center from the adverse effect of the pressure upon its blood supply Ischemia, when not too severe stimulates practically all the medullary centers, including the vasomotor center, increased intracranial pressure therefore causes vasoconstriction and consequent elevation of blood pressure The high pressure thus produced acts upon the aorta and carotid sinus so as to initiate the depressor reflexes described above, and is therefore a secondary reason for the slowing of the heart in increased intracranial tension

It is important to distinguish between intracranial tension *outside* the cerebral vessels and the intracranial *intra-arterial* tension The former tends to compress the blood vessels and produce cerebral ischemia the latter on the contrary promotes blood flow through the brain Elevation of intracranial intra arterial tension causes slowing of the heart, but in this case the slowing is not due to any direct action of the arterial pressure on the vagus center It has been shown that this slowing disappears when all the nerves in the neighborhood of the carotid sinus have been destroyed Intra arterial pressure changes in the head therefore produce their effect upon the heart rate not through any direct action on the vagus center but entirely through reflexes generated from the carotid sinus

(5) The Cardiac Center The sympathetic and vagus centers in the

medulla together form a functional unit referred to as the "cardiac center" The quantity and quality of the blood reaching this center affect the heart rate Slight anoxemia of the "cardiac center" causes increased heart rate, as does also a small excess of carbon dioxide, very severe oxygen lack causes slowing of the heart, and a large excess of carbon dioxide leads to heart-block These effects are produced by means of appropriate efferent impulses via the vagus, the sympathetic, or both An increased temperature of the blood bathing the center accelerates the heart Increased intracranial tension from any local cause within the skull tends to reduce the amount of blood supplied to the cardiac center, the latter responding by accelerating the heart This action, however, may be checked in case the coincident stimulation of the vasomotor center raises the systemic blood pressure enough to initiate the vagus depressor reflexes described above

(6) **The Sympathetic Nerve Control of the Heart.** The sympathetic nerve control of the heart may be considered subordinate to the vagus control for two reasons (1) Under normal resting conditions, it is quite inactive (has weak tone), that is, if the normal sympathetic accelerating influence is entirely removed, the resulting slowing of the heart is slight or negligible (2) On stimulation of the sympathetic supply, the acceleration of the heart begins only after a considerable latent period and develops gradually

This type of response is relatively ineffective when there is need of prompt increase in the activity of the heart Though the acceleration produced by sympathetic stimulation sets in later than that effected by inhibition of vagus tone, it persists longer and so maintains the response initiated via the vagus Usually increased sympathetic tone simultaneously induces secretion into the blood stream of adrenalin, which still further prolongs the acceleration of the heart, the hormone effect as usual, beginning later and lasting longer than the effect produced by nerve stimulation

The center of the sympathetic efferent nerves is the medulla, though its exact site in the floor of the fourth ventricle is unknown The afferent paths by which impulses may reach and affect it are identical with those already mentioned in connection with the vagus cardiac center, that is, afferent nerve fibers of all types from everywhere in the body Likewise, the special cardiovascular sensory regions (right auricle, root of aorta, carotid sinus) related to vagus control have a similar intimate relation with the sympathetic control Thus acceleration of the heart from overdistention of the auricle, though largely brought about by inhibition of the vagus center as described above, is partly accomplished by

stimulation of the sympathetic nerves, and slowing of the heart via the vagus in the depressor reflex is assisted by a simultaneous decrease of sympathetic tone However, in most cases, the major portion of the total response is mediated through the vagus and very little through the sympathetic Anatomically the sympathetic nerve fibers to and from the heart pass through the stellate ganglia and bilaterally T_1 through T_4 thoracic ganglia Of the two sides, the right side seems to be the more important

Blood Supply of the Heart The blood supply of the heart muscle is directly dependent upon the aortic pressure, especially during diastole, since most of the flow through the coronary vessels occurs during the relaxation phase of the heart cycle Vasomotor nerve control of coronary blood flow is very inconspicuous under normal conditions even though the vessels have been shown to be supplied with constrictor dilator fibers When the aortic pressure falls to a very low level due to loss of peripheral resistance, as in spinal anesthesia, the blood supply of the heart is markedly curtailed and the heart suffers from anoxemia This often expresses itself by precordial pain, which may have the character and radiation found in cases of coronary occlusion. Severe anoxemia of even a normal heart cannot be regarded as unimportant and, if persistent, may be expected to induce or aggravate the condition of shock Since the oxygen supply of the heart depends upon the coronary blood flow and the latter is proportional to the intra aortic pressure, a marked and persistent lowering of blood pressure from any cause is not to be viewed with equanimity This is true of spinal anesthesia, regardless of the fact that numerous patients have survived after their brachial blood pressure had been so low as to be unobtainable for a considerable period. Transfusion of whole blood directly into an artery may at times be lifesaving when intravenous transfusion would be of no avail This is presumably true because the intra arterial transfusion corrects the myocardial ischemia before demanding that the heart pump more blood through its ventricles

The coronary arteries are not exactly end-arteries anatomically, as there is some anastomosis between them, but functionally this anastomosis is inadequate in the face of sudden occlusion Hence it is not safe to ligate a trunk or main branch of a coronary artery However, this may have to be done regardless of consequences if the vessel is severed for an open blood vessel is of no more use to the circulation than one which is ligated

Chronic disease of the coronary arteries is within the scope of surgical therapy in some cases Several methods of operative treatment at pres

ent are available (1) Sympathectomy, consisting of stellate ganglionectomy and thoracic ganglionectomy, T_1 through T_4, which may be either unilateral or bilateral, for cases in which vasoconstriction and pain are prominent and in which rather advanced disease precludes more formidable procedures Fauteux has advocated that the denervation be done directly upon the coronary arteries, rather than the sympathetic plexus (2) At one time thyroidectomy was advocated to decrease the demands on the coronary circulation by lowering the basal metabolic rate This operation has been given up because of the side effects of total thyroidectomy Chemical thyroidectomy with thiouracil derivatives has about the same effects as surgical thyroidectomy except that it is reversible and simpler to do (3) Obstruction of the venous outflow of the coronary vessels has been advocated in cases of coronary artery insufficiency, the rationale being that the obstructed coronary artery will be back perfused from the venous side This alone has not had wide clinical usage but has recently been advocated in conjunction with construction of collateral blood supply (4) Construction of a collateral blood supply may be attempted in several ways Beck previously advocated placing asbestos in the pericardial sac in an effort to promote vascular adhesions to revascularize the heart from the pericardium O'Shaughnessy introduced the idea of revascularizing the heart, using adhesions between the heart and the omentum which was brought up through the diaphragm (5) More recently Beck in man has anastomosed an arterial graft from the aorta to the coronary sinus and ligated the coronary sinus to prevent venous outflow This method introduces arterial blood into the obstructed venous side of the coronary circulation and in experimental animals, at least, back perfuses the obstructed coronary artery More clinical work will have to be done to evaluate the place of this operation in patients with coronary thrombosis

Cardiac Arrest and Cardiac Massage—Ventricular Fibrillation: In experimental animals abnormal stimuli of various kinds, such as kneading and strong electric shock applied to the heart often induce abnormal rhythms, particularly ventricular fibrillation from which recovery is usually impossible This susceptibility to ventricular fibrillation varies greatly in different species It is apparently very slight in man, for experience has shown that the heart may tolerate wounds if not too severe and the application of sutures and the manipulation incident to various intrathoracic operations However, the possibility of ventricular fibrillation resulting from the massage of the heart for

cardiac arrest exists Therefore, the procedure should only be undertaken when it is quite certain that the spontaneous beating of the heart has actually ceased

Causes of Cardiac Arrest The heart ceases to beat only for good and sufficient cause If the cause is known it is usually obvious whether or not any benefit can reasonably be expected from cardiac massage Obviously the latter is not indicated where the stopping of the heart is the terminal event in some fatal condition, for example, advanced carcinomatosis In general the procedure is only considered with reference to functional cardiac arrest occurring during the course of operation for some extracardiac condition There are no doubt, many other instances where cardiac massage could be applied, but the problem is that of getting at the heart within a few minutes after the heart has stopped Unless the patient is in the operating room, the chances of being able to massage the heart manually within the necessary few moments is apt to be unlikely

It is possible for a patient with diseased coronary arteries to suffer a grave coronary occlusion while undergoing an operation, either purely as a coincidence or partly because of the extra strain imposed upon the heart at the time. In such a case, massage of the heart is not very promising, but should be done The age of the patient, the existence or likelihood of previous organic disease of the heart and the absence of any other apparent cause for the cardiac arrest would partially be determining factors in the success of the massage In general, however, cessation of the heart beat due entirely to organic disease of the heart is not likely to occur often during surgical operation Some temporary event connected with the operation will usually be found to be the cause of the asystole under such circumstances

Cardiac Arrest and Anesthesia Anesthesia is probably the most common cause of cardiac arrest during operation Yet there is much uncertainty in this connection Practically all the agents now employed for general and local anesthesia cause serious depression and in some cases even total paralysis of respiration before they produce any very marked deleterious effect upon the circulatory system. The same is true of the common pre-anesthetic drugs and also of oxygen lack Ordinarily, therefore, respiratory depression is manifested before cardiac arrest occurs This is the usual sequence of events, and if the cause is removed and adequate breathing is restored promptly enough by appropriate measures, cardiac arrest does not occur If, however the preceding respiratory failure is not noted until cessation of the

heartbeat is about to occur or has occurred, artificial respiration alone will not be followed by recovery of the heartbeat Under such circumstances prompt massage of the heart may be effective

Anoxemia and Acapnia: If rapidly administered, a large overdose of most of the volatile anesthetic agents may seriously disturb the circulatory and respiratory systems at nearly the same moment, or may even affect the circulation somewhat earlier than the respiration The same is true of sudden severe anoxemia, particularly under certain circumstances One might think of sudden complete occlusion of the trachea as a condition inducing the most sudden and most marked degree of anoxemia possible, but this is not so After such occlusion the residual air in the lungs is still available for a short time A more sudden anoxemia is induced if a gas or gas mixture containing no oxygen is rapidly respired, particularly if rebreathing is prevented Under these circumstances much of the residual air in the lungs with its contained oxygen is diluted and expelled at the very same time that all new supplies of oxygen are shut off Also the disturbance of carbon dioxide values is of importance in this connection Simple occlusion of the trachea is followed by increased respiratory efforts and rise of blood pressure, stimulation of the two vital systems being due mainly to the rapid accumulation of carbon dioxide in the blood Asphyxia from respiration of oxygen-free gas was thought to be associated with a marked fall in the carbon dioxide concentration in the blood, for the respired gas washes carbon dioxide out of the lungs, and it was felt that the tissues could not form any more carbon dioxide for lack of oxygen Carbon dioxide is a beneficent substance, of importance for the regulation of respiration and vasomotor tone and also influencing the normal action of the heart For this reason carbon dioxide was formerly added to oxygen used in resuscitation to ensure adequate carbon dioxide in the blood This has been abandoned, for in all instances the body will make enough carbon dioxide of its own In addition, when carbon dioxide reaches 10 per cent by volume it is a narcotic which may be dangerous

All the noxious factors mentioned above, namely direct toxic action on the heart, shutting off of new oxygen supplies, washing out of residual alveolar oxygen and removal of carbon dioxide may be combined in some cases of improperly given inhalation anesthesia The agent may be given in large overdosage and too rapidly, the supply of oxygen may be reduced suddenly to a very inadequate level and the carbon dioxide content of the blood may be lowered Under such circumstances life cannot long endure in any of the tissues, and cardiac

arrest is simply a cessation of function which happens to be easier to detect than others occurring throughout the organism at the same time.

3 **Vascular Failure and Cardiac Arrest.** When anesthesia, anoxemia or any other factor connected with an operation causes grave impairment of the circulation during the procedure, even to the extent that the heartbeat cannot be detected, the primary disturbance is vascular much more often than it is the cardiac factors discussed above. The noxious agent in most instances causes paralysis of the vasomotor center and consequent relaxation of the blood vessels before it affects the heart directly to the extent of causing cessation of its beat. Seldom if ever in these acute episodes does the direct effect upon the walls of the vessels outweigh in importance the central vasomotor disturbance.

A serious grade of true surgical shock, which is a disorder of the capillaries themselves, seldom becomes manifest during the course of an operation unless it was present or imminent before the operation. When the vasomotor collapse occurs, the heart may still continue to beat for a short time (minutes or several hours) after its pulsations are no longer perceptible by ordinary clinical means including auscultation. Therefore, unless there is other evidence that the heart has actually ceased to beat, such as may be obtained in cases in which the thorax or abdomen is open, the chief indication is to restore vascular tone rather than cardiac systole. Unless this is accomplished promptly the heart of course will soon cease to beat for lack of its coronary circulation, but if blood vessel tone is restored, the necessity for cardiac massage does not arise.

Chloroform and ethyl chloride (by inhalation) are two exceptions in that their direct depressing effect upon the heart seems to be more severe than that upon the vasomotor center. With these agents, therefore, there is presumably greater possibility of circulatory failure of the type in which cardiac massage may sometimes be indicated—that is, the type with which a high mortality is inevitably associated.

4 **Reflex Cardiac Arrest.** It is said that cardiac asystole sometimes occurs purely as the result of a disturbance in the extrinsic nervous control of the heart, that is as a reflex phenomenon, abnormal nerve impulses impinging on the heart and abolishing in some way the generation of impulses in the sinoauricular node. It is unlikely that this ever occurs in a heart which is organically sound, in view of the fact that not only the sinoauricular node but also all other parts of the heart muscle are capable of initiating rhythmic impulses in the absence of all extrinsic nerves. If such a case should actually occur, cardiac massage would be indicated.

anesthetist can breathe for the patient by squeezing the mixing bag It is the surgeon s responsibility to expose the heart quickly, preferably through the chest If a thoracic operation is in progress this presents no difficulties

If an operation is being done elsewhere, adequate exposure of the heart can quickly be made by cutting into the thorax through the fifth left interspace, cutting the fifth and sixth cartilages and spreading the incision with a self retaining retractor This will permit massage of the heart In many instances the mechanical stimulus of several squeezes may start the heart beating again spontaneously However, rhythmic, steady massage of about 40 times per minute must be maintained continuously until the heart beats by itself This will maintain cerebral and coronary circulation In fact the anesthetist should check for a carotid pulse A weak brachial pulse will probably be felt Maintenance of effective blood volume is important at this time Vasoconstrictor drugs and possibly an intra arterial transfusion are in order to keep proper proportions of blood volume versus vascular bed Attempts to resuscitate the heart should be continued for a considerable period of time or until there is certainty that higher cerebral centers are dead

The real emergency is getting oxygen into the lungs and massage of the heart instituted promptly before irreversible changes have taken place in the brain Only about three to four minutes of absent circulation will be tolerated by the higher cerebral centers Inspection of the heart may reveal that ventricular fibrillation is present or it may be precipitated in the efforts at resuscitation At times rapid tachycardia may simulate ventricular fibrillation and has no doubt been responsible for the reported successes in the literature of defibrillation by massage alone If there is question about the presence of ventricular fibrillation, one should have time to take an electrocardiograph tracing while massage is being maintained to see if there is a fibrillating complex coming through If ventricular fibrillation is present about the only hope for resuscitation of the patient lies in the application of an electrical shock to the myocardium in such fashion that the whole heart is put into contraction at once following which it may relax and resume its normal beat Suitable electrodes are applied to either side of the heart and an alternating current of one and a half ampere, 110 volts, applied for a brief burst of about a tenth of a second, although it may have to be applied several times If chemical agents are used, they should be injected into the blood vessel of the auricle not through the ventricle wall At times, ventricular fibrillation has no doubt been precipitated by injudicious needling of the ischemic myocardium

On the other hand, at times cardiac arrest has been re-started by the

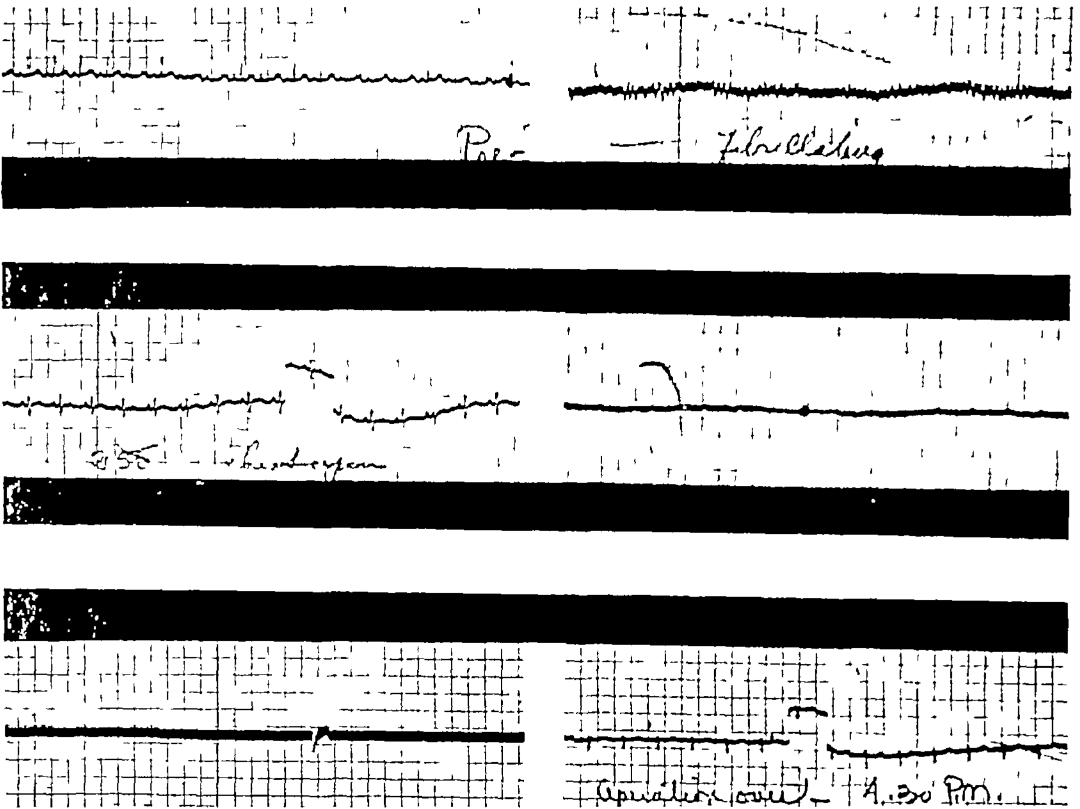


FIG 4 Electrocardiograms made experimentally on the dog Limb Lead II is used throughout UPPER LEFT tracing taken preoperatively MIDDLE LEFT tracing taken with chest opened LOWER LEFT tracing taken after a period of anoxia UPPER RIGHT tracing shows ventricular fibrillation provoked by ligation of the ramus decendans branch of the left coronary artery and injection of adrenalin into the myocardium of the left ventricle MIDDLE RIGHT tracing shows a regular beat again after injecting two cubic centimeters of two per cent novocain into the left auricle and shocking the heart electrically LOWER RIGHT tracing, taken after the chest was closed, shows a relatively normal tracing

traumatic needling of the myocardium The dangers of ventricular fibrillation are so great that passing needles through the ventricular myocardium of the ischemic heart should be considered hazardous Various workers have advocated the use of novocaine in the pericardial sac or in the blood vessels or auricle to lower the irritability of the heart in preparation to shocking the fibrillating heart Adrenalin has been used to increase myocardial contraction and increase vasomotor tone The prognosis in cardiac arrest is good if early massage and oxygen are administered The prognosis in ventricular fibrillation is poor, but it is not hopeless if it is recognized and oxygen and massage are instituted early and if proper shocking procedures are available The first successful case with electrocardiographic proof of ventricular fibrillation treated on the operating table was reported by Beck in

1947 "Successful" resuscitation must always result in an alive, apparently normal subject Figure 4 illustrates fibrillation treated experimentally in the dog

THE PERICARDIUM

Adherent Pericardium The chief function of the pericardium, like that of other serous membranes, is to reduce friction However, it is not essential to life for it has been found absent in apparently normal individuals When the visceral and parietal layers are adherent, the movements of the heart may be embarrassed to some extent, though this impediment is not usually a serious one But when such intrinsic pericardial adhesions are associated with extrinsic adhesions, that is, abnormal adhesions between the parietal pericardium and the surrounding structures, particularly the rigid thoracic cage, the beating of the heart may be very seriously impeded (Accretio cordis) Difficulty sometimes is due in large part to firm encapsulation of the heart by a rigid layer of fibrous tissue which checks diastolic filling, in such a case decapsulation must be performed in addition to cardiolysis (Concretio cordis) Figure 5

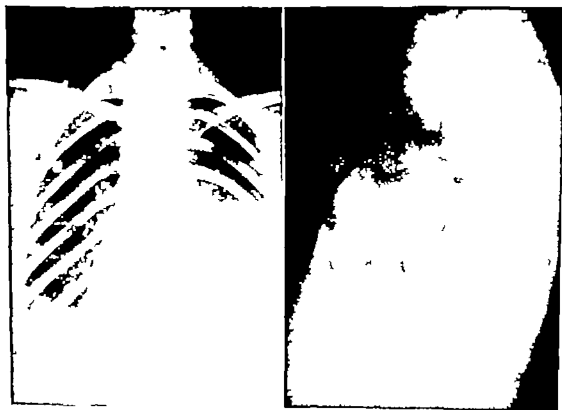


FIG. 5 Postero-anterior and lateral x ray views demonstrating a rim of calcium which constricted the heart The patient was treated successfully by surgery

Pericardial Effusion When the peripheral sac becomes distended with exudate very gradually, the parietal layer enlarges somewhat and may accommodate 1000 cubic centimeters or more of fluid When the effusion collects rapidly, the pressure within the sac rises and may impede venous filling of the heart since the venous pressure at the heart is normally very low. If blood under arterial pressure escapes into the pericardial cavity, as in rupture or wounding of the heart or root of the aorta, a similar but as a rule rapidly fatal heart-tamponade occurs, the high intrapericardial pressure entirely preventing venous blood from entering the heart

Pneumocardiac Tamponade There is a basic negative pressure within the pericardium equal to the general intrathoracic negative pressure, and produced by the same cause as the latter, namely the constant retraction-tendency of the lungs This basic negative pressure alternately decreases (becoming more negative) and increases (becoming positive) with inspiration and expiration respectively, just as intrapleural pressure continually varies Therefore, if a free communication is made between the pericardial cavity and the atmospheric air, air is sucked in during inspiration and forced out during expiration exactly as occurs in the pleural cavity in cases of open pneumothorax In the former instance there is much less interference with respiration by direct displacement of lung tissue because of the limited volume of air which the pericardium can admit But there is a certain mild heart-tamponade effect, by reason of the fact that the pressure-environment of the heart is changed from its normal subatmospheric level to atmospheric pressure This is equivalent to a corresponding degree of compression of the heart and though the actual pressure-change amounts to only a few millimeters of mercury, it is sufficient to impede the filling of the heart somewhat, because the pressure under which the blood enters the heart is not much higher Of itself such an open pneumopericardium tends to counteract the effective venous pressure responsible for filling of the heart, but Beck and Cox found in animals that there occurs a compensatory sustained rise in venous pressure They also found a transient fall of arterial pressure of slight or moderate degree and a 15 to 30 per cent decrease in minute output of the heart, and use the term pneumocardiac tamponade to designate the condition

Acute Cardiac Compression Beck has described clearly the differences between the effects of acute and of chronic cardiac compression An acute increase in intrapericardial pressure causes the venous pressure to rise by as much as 15 centimeters of water The increased

pressure on the venous side of the heart initiates the Bainbridge reflex (the temporarily decreased aortic pressure has the same effect) stimulating the cardiac and vasomotor centers so that arterial pressure is maintained as near normal as possible These responses particularly that of the vasomotor center are so effective that when the amount of blood entering the heart is reduced as much as 50 per cent below normal the arterial pressure may show little if any diminution The veins do not become prominent probably because of reflex increase of their tone Ascites hydrothorax and edema do not appear because the condition is of too short duration In such a case it is obvious that the heart output and hence the effective circulation must also be reduced by 50 per cent The arterial blood pressure therefore, fails to indicate this deficiency As the circulatory failure becomes more marked, the skin becomes cold pale and moist because of extreme sympathetic stimulation trying to balance a falling heart output by raising peripheral resistance When arterial pressure can no longer be maintained even in a restricted portion of the body, anemia of the brain occurs and leads to loss of consciousness

Chronic Cardiac Compression Much higher intrapericardial pressure can be tolerated if the pressure increases gradually, because there is time for the development of compensatory mechanisms the most important of which is the building up of high venous pressure The latter may become as high as 30 to 34 centimeters of water The veins become visibly distended probably because of the prolonged pressure within them The pericardium enlarges gradually, the liver and spleen become enlarged due to congestion, and hydrothorax and ascites develop In contrast to the ordinary type of congestive heart failure, subcutaneous edema is not marked and appears late the reason for this difference is unknown Cyanosis, weakness and dyspnea on exertion occur Systolic blood pressure is low because of the small stroke volume, diastolic pressure remains near the normal level so that the pulse pressure is reduced The per minute volume output is diminished Vital capacity is decreased

Normally, on inspiration more blood enters the chest and then enters the heart This results in a stronger pulse in the peripheral arteries Conversely, on expiration less blood enters the chest and less enters the heart Relatively, the peripheral pulse is weaker on palpation

In cardiac tamponade the reverse may be true The best explanation of this phenomenon is as follows When the intrathoracic pressure lowers on inspiration, the pressure in the pericardium remains high

and the diastolic filling is less, so that the pulse weakens On expiration, the intrathoracic pressure becomes more positive and the effective diastolic filling pressure increases also. This causes the pulse to strengthen on expiration

Beck has designated as the "acute cardiac compression triad" the syndrome consisting of (1) a falling arterial pressure, (2) a rising venous pressure, and (3) a small quiet heart, and as the "chronic cardiac compression triad" the combination of (1) a high venous pressure, (2) ascites, and (3) a small quiet heart (Figure 6)

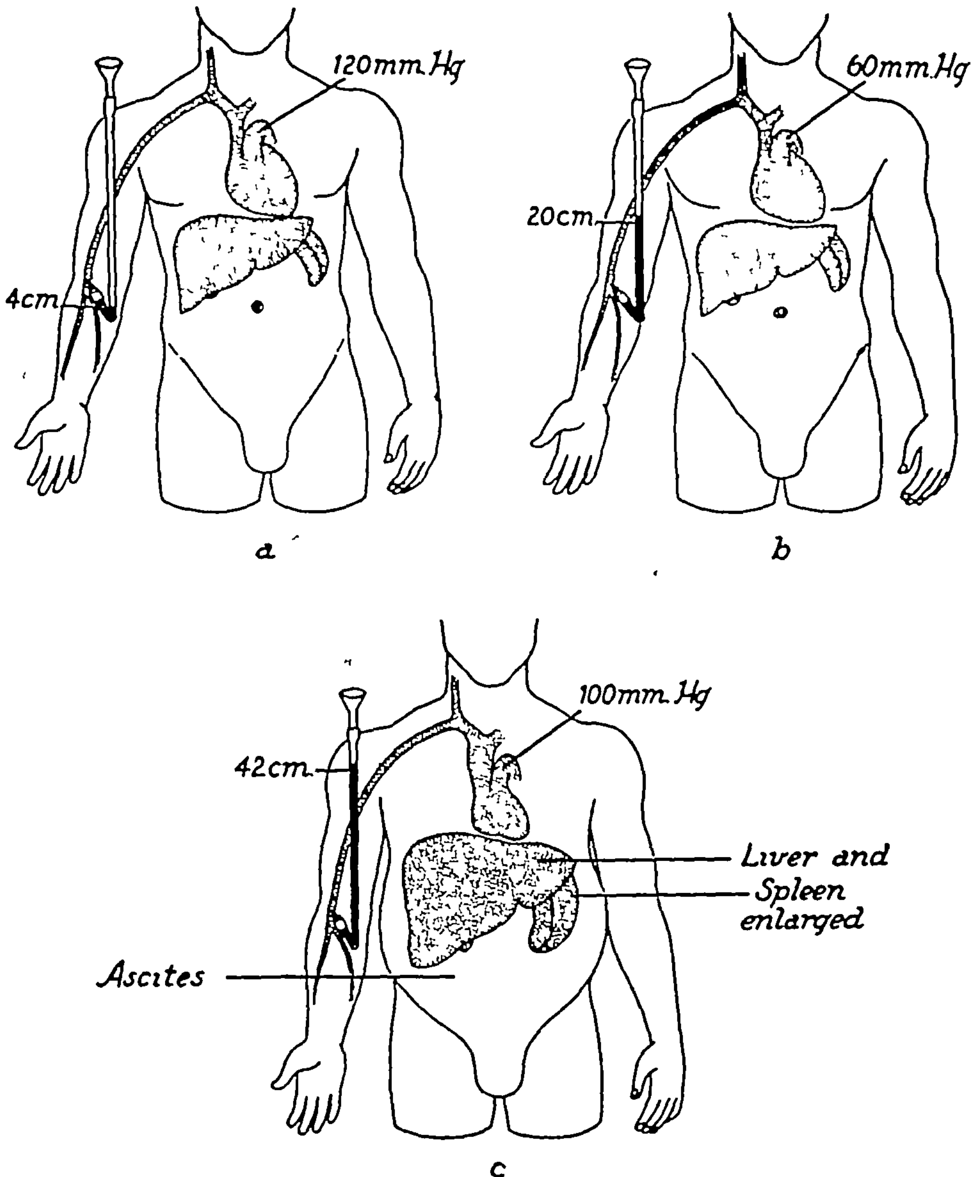


Fig 6 Acute and chronic cardiac compression triads (a) Normal (for comparison) (b) Acute cardiac compression Falling arterial pressure, rising venous pressure, small quiet heart (c) Chronic cardiac compression High venous pressure, ascites, small quiet heart (From Beck)

Circulatory failure due to chronic intrapericardial pressure from fluid or scar tissue can often be relieved by operation Beck and Griswold studied the effects of pericardiectomy in the treatment of the Pick syndrome by producing the condition experimentally in dogs by the use of surgical solution of chlorinated soda Beck and Cushing and also others, have employed the operation successfully in man

Arterio venous aneurysms place an extra load upon the circulation The cardiac output is elevated roughly in proportion to the size of the fistula When the fistula is closed there occurs a slowing of the pulse rate, known as Branham's bradycardic phenomenon It is due to stimulation of the vagus center as a consequence of the sudden rise in blood pressure Usually there is a rise of both the systolic and the diastolic pressure the latter is permanent when the fistula is closed surgically, whereas the systolic pressure may return to the preoperative level These fistulae may be congenital or acquired Increased growth of the affected extremity sometimes occurs especially in cirsoid aneurysms, which are usually congenital In traumatic arteriovenous aneurysm Reid and McGuire advise a delay of operation for three to six months, in general This favors development of collateral circulation in case division of the artery will be necessary at the time the fistulous connection is closed However, a rapidly rising venous pressure is an indication for early operation even though the heart seems clinically not badly affected If an arteriovenous aneurysm of large size is allowed to persist, there will be an ultimate failing of the heart due to the increased cardiac output that the heart will be called upon to maintain If the heart be healthy, this failure may take a considerable number of years to develop

THE BLOOD VESSELS

The second part of the circulation consists of the blood vessels, which are divided into two sets, the pulmonary and the systemic The left ventricle pumps blood into the great arteries and on into the smaller arteries of the systemic circulation The physiology of the systemic blood vessels will be discussed in detail in Chapter III

The Systemic Arteries In order that the pumping action of the heart may be effective in maintaining pressure within the vascular system, it is necessary that there be opposed to it a permanent resistance otherwise the blood ejected by the heart would flow with a very high velocity but under a negligible pressure The blood vessels offer the required resistance, familiarly known as peripheral resistance

The larger arteries including the aorta oppose the flow of blood through them to but a very slight extent since their caliber is relatively

large Therefore they take little part in determining the systolic blood pressure, that is, the level to which the blood pressure rises at the time the heart is contracting But the large arteries are a prominent factor in determining the diastolic blood pressure, in fact they may be considered the essential cause of the presence of any pressure during diastole Since their walls have considerable elasticity, and the smaller vessels situated more peripherally offer a great deal of resistance to the onflow of blood, the large arteries become distended by the blood ejected during systole, accommodating it until it is able to pass on into the narrower vessels The end of systole finds the large vessels overfilled with blood and their walls stretched, the tension of the stretched elastic walls pressing on the contained blood accounts for the pressure maintained during diastole

The Pulmonary Blood Vessels The pulmonary blood vessels—arteries, capillaries and veins—differ from the systemic vessels The pulmonary arteries are short, branch quickly and carry blood under lessened pressure The capillaries of the lung are unique in that they are surrounded and exposed to approximately 140 square meters surface area of air The veins are short and thin-walled During inspiration their pressure falls below atmospheric pressure, so that if a hole be made in the vein, air can be sucked into the vein As little as one cubic centimeter of air in a pulmonary vein may be shown to be fatal in experimental animals Death is more likely to occur if the air bubble enters a coronary artery A bubble in the cerebral circulation is less dangerous than a bubble in the coronary circulation If it is suspected that air has entered the pulmonary vein, raising the head of the patient to keep bubbles out of the coronary circulation is probably more valuable than lowering the head, which facilitates the entry of the bubble into the coronary circulation

Air emboli in the right ventricle and lungs will not cause death in most instances unless several hundred cubic centimeters of air are injected into a systemic vein The amount of air tolerated will depend upon the speed of injection The air trapped in the right auricle and right ventricle interferes with the pumping action of the heart, and death may follow the injection Bubbles of air in the pulmonary arterioles and capillaries cause dyspnea, cyanosis, and anxiety, usually with a sensation of tightness in the chest

The amount of blood in the pulmonary circulation varies with the phases of respiration On inspiration, about 9 per cent of the total blood volume is in the lungs, whereas during expiration, only 6 per cent of the total blood volume is in the lungs In pathologic states where the

outflow of blood from the pulmonary circulation is obstructed, i e, mitral stenosis the blood in the lungs increases markedly until twenty per cent or more of the total blood volume is in the pulmonary blood vessels The engorged lungs in the latter instance become like erectile tissue, are rigid ventilate poorly and contain less air The pulmonary vessels adapt themselves rather readily to various amounts of blood, due largely to their location in lung tissue which adjusts to changes better than more solid tissues Increased pressure in the veins is soon transmitted back to the arteries The cardiac catheter permits measurements of pressure in the pulmonary arteries in health and disease in the intact human patient

Pulmonary artery pressures have been compared in normal subjects and in patients with chronic pulmonary disease by Riley *et al* The normal individual after exercise which is sufficient to raise the cardiac output two to three times normal values, still has a normal pulmonary artery pressure This could only mean that there is a decreased pulmonary vascular resistance during exercise The mechanism causing this decrease in resistance is obscure It might be due either to opening more widely the vessels in use or else bringing into use more vessels In contrast, patients with chronic pulmonary disease tend to have resting pulmonary artery pressures (both mean and systolic) above normal With exercise, there is a further increase in the pulmonary artery pressures In one instance, a systolic pressure of about one hundred millimeters of mercury was reached after exercise in a patient with chronic pulmonary disease This seems to be caused by loss of expansibility of the pulmonary vascular bed in chronic pulmonary disease Emphysema reduces the available capillary bed through its destruction of alveolar walls Pulmonary fibrosis apparently causes a fibrotic constriction which diminishes the expansibility of the pulmonary vessels in the interstitial tissue

Another factor which affects the pulmonary vessels is the intra alveolar pressure This has important implications in relation to anesthesia for thoracic surgery If the pressure be elevated in the anesthesia machine the pressure of gas in the lungs increases and the pressure in the pulmonary artery increases, no doubt due to the increased resistance in the pulmonary vessels Ten millimeters of mercury rise in pressure in the anesthesia machine, raises the mean pulmonary artery pressure 10 to 15 millimeters of mercury (in the dog) Consequently, if excessive positive pressure is maintained in the airway, the right heart could be embarrassed and a fall in cardiac output would result To some degree this phenomenon occurs when acute pulmonary edema

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arteries and the pulmonary arteries in the region of the lobar or segmental bronchi In bronchiectasis they found large anastomoses developed at the level of the third or fourth order bronchi

These anastomoses would seem to shunt a considerable amount of blood into the pulmonary circulation if one considers their size and the fact that the bronchial arteries carry blood under systemic pressures In the dog it has been estimated that the normal bronchial artery carries about 27 cubic centimeters of blood per square meter body surface per minute Bloomer *et al* studied the dog with a ligated left pulmonary artery In such an instance, the bronchial circulation enlarges enormously They estimated the bronchial artery blood flow to be in the order of 900 cubic centimeters per square meter body surface per minute

It seems clear that large anastomoses can develop between the bronchial arteries and pulmonary arteries at a precapillary level It would seem logical to suppose that some of the oxygenated bronchial artery blood might drain towards the heart in the pulmonary arteries This would be particularly obvious if the disease were unilateral and if there were obstruction to drainage through the pulmonary veins This might explain why patients with severe unilateral bronchiectasis can have high systemic arterial oxygen saturation (Liebow) It also seems possible that these bronchial artery anatomoses can be the source of a good sized left to right shunt This would in theory place an extra load on the left ventricle

It had been thought that ligation of a lobar pulmonary vein would cause destruction of the lobe Swan found in dogs, that division of a lobar pulmonary vein caused intense edema of the lobe, hemorrhage into it and thrombosis But after several months new collateral venous channels developed across the pleural space to the systemic circulation, the lobe improved and seemed to be scarred, but was otherwise relatively normal In this situation it seems possible that the bronchial artery emptying into the pulmonary artery might be the factor saving the lobe whose vein was divided The pulmonary artery can be ligated without resultant destruction of the lung The lung will no longer oxygenate its share of venous blood but the bronchial artery will apparently suffice to nourish the lung parenchyma Ligation of the pulmonary artery and the pulmonary vein to a lung or lobe will be followed by gangrene of the lung Ligation of the bronchial artery alone in the human will be followed by no apparent ill effects due to rich collateral bronchial circulation This happens at times when extrapulmonary tumors in the region of the bronchial arteries are removed

is treated by interposing two to three centimeters of water pressure resistance to expiration The increased pressure in the airway helps prevent transudation of more fluid into the alveoli partly because the increased resistance in the pulmonary arteries causes a reduction in the amount of blood pumped into the engorged lungs by the right ventricle

Vasoconstrictor and vasodilator fibers both have been described in the sympathetic and parasympathetic nerve supplies to the pulmonary vessels Anatomically, in man, the nerve supply to the arteries is greater than to the veins The nerve supply to the left pulmonary artery is greater than to the right pulmonary artery The full role of these nerves in controlling pulmonary circulation in man has not been clarified, as has already been mentioned in the discussion of pulmonary embolism

Pulmonary artery hypotension occurs also Surgically, it will be met most commonly in severe hemorrhage In pulmonary hypotension due to hemorrhage, hypotension will of course exist in the systemic circulation and be much more obvious It may be that future studies may discover some significance of pulmonary hypotension Most diseases under study at the present do not change pulmonary artery pressures, or else cause a rise in pulmonary artery pressure

The Role of Bronchial Artery Circulation This chapter has divided circulation into two parts pulmonary and systemic The bronchial circulation is unique in that it begins in the systemic circulation, but for the most part drains into the pulmonary circulation The bronchial arteries take origin from the aorta and carry oxygenated blood at systemic pressures to the pulmonary tissue There are bronchial veins, which drain into the azygos system, but apparently they carry little of the bronchial artery blood back into the systemic circulation Most of the bronchial artery blood drains into the pulmonary veins

The bronchial arteries (Miller) run only to the terminal bronchioles in the normal human They are the vasa vasorum of the pulmonary arteries and supply the walls of the bronchi In the normal human (Miller) the vascular connections between the bronchial and the pulmonary circulation occur only at capillary levels In pathological states of the lungs, precapillary connections between the bronchial and pulmonary circulations do occur Wood demonstrated these precapillary anastomoses in numerous disease conditions Liebow *et al* have recently studied these anastomoses in certain disease states In congenital pulmonic stenosis, they found large anastomoses between the bronchial

electrolytes. Ingested *water* is rapidly distributed to the tissues and subsequently excreted, the immediate aim being to maintain the normal osmotic status of the blood The process is not primarily for the adjustment of blood volume, but it accomplishes this result at the same time that it restores normal osmotic pressure Abstinence from water, on the contrary, results in increased concentration of hemoglobin in the blood, increased viscosity and osmotic pressure and ultimately a fall in blood pressure due to decreased blood volume When excessive blood concentration was produced by plasmapheresis in animals, Harkins and Harmon found that the amount of plasma which needed to be removed to cause death was equal to four per cent of the body weight.

Rapid injection of saline solution intravenously scarcely increases the blood volume appreciably, as the added fluid is quickly eliminated from the circulatory system even if the action of the kidneys is excluded

In cardiac patients or in patients who have a left ventricle ready to go into failure, sudden overloading of the circulation, particularly with hypertonic solutions, may have deleterious effects and cause acute pulmonary edema Intravenous infusion of large volumes of solution given rapidly may be dangerous In known cardiac patients, subcutaneous or intramuscular infusions are to be preferred

It is difficult to alter markedly the concentration of the blood, particularly of the serum, by administration of fluid or salts by any route The concentration decreases to some extent after the ingestion of a large amount of sodium chloride, because the salt draws water from the tissues into the circulation After hemorrhage, the blood concentration decreases because of a similar intake of water from the tissues, by some unknown mechanism, for the purpose of restoring blood volume Variations in the concentration of solids in the blood serum are mainly due to variations in the per cent of proteins (except when the non protein nitrogen is high) for the concentration of the chief salt, sodium chloride, is relatively fixed

When an *isotonic neutral salt solution* is ingested or is injected by any route, the disturbance in blood and plasma volume is scarcely perceptible because there is an almost immediate adjustment. The Alarm Reaction (Selye) alters markedly the response to saline administration Chapter XIII will discuss the alterations seen in Stress An isotonic sugar (glucose or sucrose) solution is eliminated from the blood just as rapidly as saline and by the same mechanism

Hypertonic neutral salt solutions increase osmotic pressure and hence blood volume temporarily, fluid being drawn from the tissues into

From the hypotheses of pulmonary and bronchial artery circulations described above, one can see that the results in pulmonary embolism may be variable and much will depend upon the site of the vascular obstruction The double arterial circulation makes it possible for the lung parenchyma to survive considerable embolization of its pulmonary artery.

The Blood· The blood itself is a factor in determining the level of the blood pressure because of the influence of the three important elements—blood volume, osmotic pressure of the blood and blood viscosity

Blood Volume The amount of blood in the body is the foremost consideration Other circulatory factors remaining constant, an increase in the total volume of blood within the system tends to elevate the blood pressure and a decrease tends to lower the blood pressure Actually, of course, whenever there is an increase in blood volume, the other circulatory factors do not remain constant but immediately begin to compensate for the changed condition The surgeon is seldom concerned with clinical conditions associated with excessive total blood volume but is constantly dealing with conditions associated with diminished blood volume, the most obvious one being hemorrhage, in which the diminished blood volume is the most important factor responsible for the clinical picture The introduction of radio-active iron isotopes for measuring red blood cell mass plus dye methods of measuring plasma volume offer relatively accurate methods of determining total blood volume It is approximately equal to seven per cent of the body weight An average sized adult has about five liters of blood The blood volume (also plasma volume) is more nearly proportional to the body surface area than to the body weight The cells constitute about 45 per cent of the blood volume. The number of blood cells in circulation depend partly upon the balance between production and destruction of cells and partly upon the state of the capillaries everywhere (dilation, permeability) and of the storage beds, namely the liver, spleen, and bone marrow

Effect of Administered Fluids on Blood Volume When additional *blood* is transfused into a normal individual, the tendency to increase the volume of circulating blood is quickly offset by loss of fluid to the tissues, so that there is an increase in the percentage of hemoglobin The extra cells are then gradually removed from the circulation by the reticulo-endothelial system

The volume of the circulating plasma is affected by the amount of water and electrolytes supplied to the body and the nature of the

hemoglobin, cell count, cell volume and plasma protein values may be at or above normal, when fluid can be taken after relief of the obstruction these decrease and the anemia present may only then become evident in the blood examination

In *venous obstruction* the capillaries in the affected region permit fluid to escape through their walls, and the venous blood becomes more concentrated than normal, its percentage content of cells, hemoglobin and proteins being increased The plasma has been found to become 30 per cent more concentrated after five minutes occlusion of the veins of the arm when the arterial inflow was not interfered with

In certain "*blood diseases*" there is an alteration of the blood volume In hemolytic icterus the total blood volume is normal or may be reduced somewhat, while the relative amount of plasma is increased After splenectomy, both cell and plasma volumes increase, the former more rapidly than the latter, the total blood volume finally exceeding the normal Splenic anemia is associated with a somewhat increased blood volume but the cell volume is below normal, after splenectomy, the blood volume falls at the expense of the plasma.

General anesthesia is regularly attended by a reduction of blood volume Administration of fluids before, during and after operation combats this effect, which tends to aggravate any coincident decrease in blood volume due to shock

Osmotic Pressure The osmotic pressure of the blood is due partly to crystalloids and partly to colloids The former are responsible by far for the greater part of the osmotic pressure However, since the total crystalloid concentration is quite even throughout all the tissues, the crystalloids do not cause any significant difference between the osmotic pressure of the blood and that of the tissues and therefore have no important influence upon the mechanics of the circulation or upon blood pressure The blood colloids (blood proteins) on the other hand less readily diffuse across the endothelial wall of the blood vessels, hence the osmotic pressure which they exert is effective in "drawing" water into or holding water within the vessels The colloid osmotic pressure of the blood therefore aids in maintaining blood pressure only by reason of its influence on blood volume When loss of blood proteins occurs, the lowered colloid osmotic pressure of the blood permits loss of fluid from the vessels to the tissues, the resulting decrease of blood volume tending to lower the blood pressure The hydrodynamic pressure, derived originally from the heart, is the force which actually causes this transudation out of the vessels

Viscosity The viscosity of the blood offers a certain amount of re-

the vessels Some of the fluid comes from the subarachnoid space, and after rapid (i e, intravenous) administration of hypertonic saline, the decrease in cerebrospinal fluid volume causes a fall in intracranial pressure Hypertonic solutions of non-electrolytes such as sugar and urea have the same effects Both types of substances, electrolytes and non-electrolytes, cause a subsequent decrease in blood volume and anhydremia, probably due to their diuretic action, since water has to be excreted in order to carry them through the kidneys

Administration of a solution of an *alkaline salt* increases the blood volume by causing hydremia The alkaline salt favors retention of fluid within the blood vessels Acidic solutions have the opposite effect, tending to cause dehydration of the blood, partly by inducing diuresis, but partly also by promoting sequestration of water in the tissues

Water and all the solutions mentioned above can penetrate cell membranes readily and so have less influence upon osmotic relations *Colloids*, on the contrary, exert an effective osmotic pressure because of the fact that they are relatively unable to penetrate cell membranes or the endothelial walls of capillaries They remain within the blood vessels and tend to draw fluid into the latter from the tissues In this way, they invariably increase the plasma volume and blood volume This effect, of course, is only obtained when the colloid is injected directly into the blood stream Colloids injected subcutaneously, or given by mouth or by rectum have no significant effect upon the blood volume and there is no rational basis for giving them by these routes for any circulatory effect

Effects of Temperature on Blood Volume: The temperature of the body affects the blood volume In fever, the general increase in body temperature causes hydremia, with increase of blood volume If sweating follows, it results in a fall of blood volume, the blood then becoming more concentrated than normal Local increase in temperature accelerates the circulation through the part so that the venous blood resembles arterial blood more closely than it usually does, but there is no recognized effect upon blood volume Cold causes local circulatory stasis, escape of fluid from the blood and concentration of the latter Possibly cold applied to a larger area causes these same changes throughout the whole body and a more marked reduction in blood volume, though this has not been established, if true, it would explain the manner in which cold aggravates the condition of surgical shock, which it is believed to do

Vomiting or diarrhea can cause very marked decrease of blood volume and hemoconcentration In cases of complete pyloric stenosis the

flow, that is, the volume of blood passing through the system per minute, rather than the pressure The only purpose of the blood pressure is to cause an adequate amount of blood to flow to and from the different parts of the body It is possible for the pressure to be high and yet the flow to be inadequate, for example, hypertension and congestive heart failure (circulatory inadequacy) not infrequently coexist The amount of blood flow per minute in the body as a whole is the same as the per minute output of the heart This factor, though of prime importance, is unfortunately difficult to measure hence it is that the blood pressure, which can easily be determined clinically, is chosen instead as the basis for the above discussion of the circulatory system

E J Beattie, Jr, M.D

sistance to the force of the heart beat and has thus an influence upon the blood pressure The column of blood in any given large vessel must be broken up into many columns of varying diameters and lengths as it advances into the more peripheral parts of the vascular tree, that is, there is a constant changing of shape of the fluid mass Viscosity may be considered as "resistance to change of shape," rather than mere "stickiness " Both the blood cells and the plasma colloids contribute to viscosity Therefore in conditions of overconcentration of the blood (anhydremia) the viscosity is increased, and tends to raise the blood pressure by increasing the resistance to flow In conditions of dilution of the blood, the lowered viscosity tends to lower the blood pressure

Circulatory Disturbances in Surgery: It is well for the surgeon to be acquainted with common irregularities of the heart such as premature contractions and auricular fibrillation, and to realize their relative unimportance as long as compensation is adequate He may thus be saved needless alarm, if for instance one of these conditions should develop suddenly during or soon after operation In general, his main interest in the heart is in its power of contractility, the physiological property which ordinarily determines its state of compensation or decompensation.

Alterations of blood pressure, particularly diminished blood pressure, dependent on disturbances of the blood vessels and of the blood are of concern to the surgeons very often Examples are spinal anesthesia (paralysis of arterioles), surgical shock (paralysis of capillaries) and hemorrhage (decrease of blood volume and viscosity)

Though it is true that in all cases of elevation or lowering of blood pressure the immediate cause is in either the heart, the blood vessels or the blood, no one element of the circulation can be disturbed without affecting in some way the functioning of the other elements The others will either be affected adversely and thereby aggravate the condition, or will take part in some compensatory reaction tending to counteract the harmful effects of the original disturbance This complex interrelationship between the various circulatory factors should be borne in mind In any given case, the important thing is to appreciate which event is primary and which events are secondary

Blood Flow: In the above account of the circulatory system, the emphasis placed upon the blood pressure should not be taken to mean that the latter is the mechanical feature of paramount importance The factors controlling *blood pressure* are stressed only as a convenient means of describing the circulation as a whole It should be understood that the really essential measure of circulatory adequacy is the *blood*

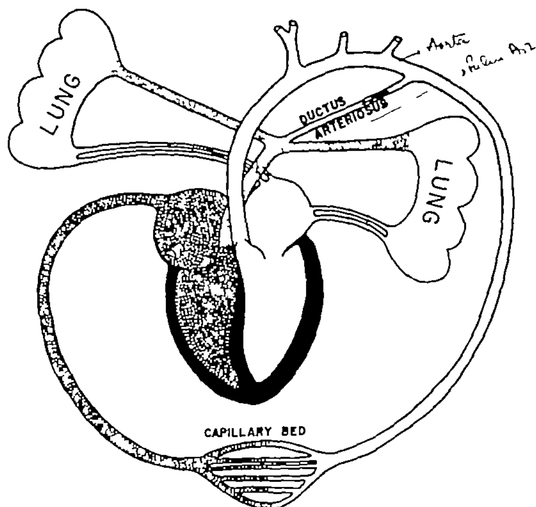


FIG. 7 Diagram of the circulation as found in an uncomplicated patent ductus arteriosus.

the amount of blood that leaks through the patent ductus arteriosus The output of the left ventricle increases and usually there is a slight falling of the diastolic pressure Consequently, there is a widening of the pulse pressure The pulmonary circulation is also given an extra load of work. Instead of maintaining the normal pulmonary artery pressure of 30 millimeters of mercury systolic over 10 millimeters of mercury diastolic, the right ventricle now has to pump against an increased head of pressure due to the leakage of blood into the pulmonary circulation through the shunt Consequently the pressure in the pulmonary artery is increased, the pulmonary arteries are dilated, the pressure in the right ventricle is increased This means that increased work is done by the right ventricle as well as the left ventricle If the patient should go into cardiac failure, there will usually be concomitant left and right ventricular failures since there is strain on both circulations Since this is a left to right shunt, unless cardiac failure supervenes or

Chapter II

RECENT ADVANCES IN THE SURGERY OF THE CARDIOVASCULAR SYSTEM

CONGENITAL DEFECTS

THE SURGICAL therapy of congenital defects in the cardiovascular system has been one of the outstanding achievements of the past decade In a large series of unselected autopsies, Gelfman and Levine found congenital vascular disease in 1 33 per cent However, the figure dropped to 0 5 per cent in those cases surviving past the age of two years This suggests that about two-thirds of the patients with congenital vascular disease succumb before the age of two

Perhaps an estimate of the relative incidence of the defects can be obtained from the list of Maude Abbott's classic *1000 Autopsy Cases,* quoted by White

(1) Interauricular septal defect—373 cases, uncomplicated in only 73 cases
(2) Interventricular septal defect—214 cases, uncomplicated in only 55 cases
(3) Patent ductus arteriosus—242 cases, uncomplicated in 92 cases
(4) Pulmonary stenosis—151 cases, uncomplicated in nine cases
(5) Anomalies of semilunar valves—146 cases
(6) Adult type of coarctation—105 cases This tends to be an isolated defect
(7) Anomalies of great veins—94 cases
(8) Complete transposition of arterial trunks—74 cases

This section will confine itself to a discussion of the congenital cardiovascular defects which have been treated surgically at the present time and also a brief discussion of those conditions which will probably next be attacked successfully

The patent ductus arteriosus consists of an arterial communication between the aorta and the pulmonary artery Since the pressure in the aorta is considerably greater than the pressure in the pulmonary artery the blood flows from the aorta to the pulmonary artery This constitutes, therefore a left to right shunt This means that the systemic circulation has to pump the amount of blood necessary for the whole body, plus

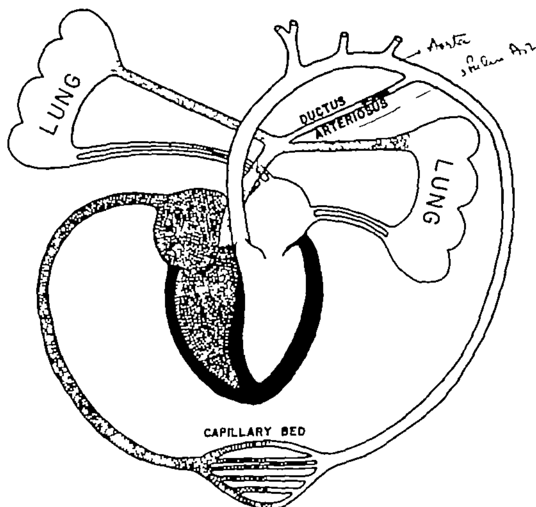


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usually not necessary unless the ductus is thought to be complicated by some other defect. In the "pure" ductus the admixture of oxygenated blood in the pulmonary artery and the elevated pulmonary artery pressure will be diagnostic

Coarctation of the Aorta is of two types, the infantile and the adult type The infantile type was so named because it was felt that infants with the lesion seldom lived to adult life In the usual infantile lesion, the stenosis is close to the left subclavian artery and is more difficult to treat than the adult type, for the adjacent subclavian artery (the chief collateral) may have to be clamped The more usual type of coarctation of the aorta, the adult type, consists of a stenosis, partial or complete, about one to two centimeters long, occurring just distal, to the left subclavian artery at the point the patent ductus arteriosus takes off from the aorta (Figure 9) However, there is overlapping in these two categories and combinations of the two occur

It has been estimated by Levine from autopsy figures that one out of every thousand persons has some degree of coarctation of the aorta Only the patients with a serious degree of stenosis will present themselves for treatment In the past, the disease has been missed all too often Now that a therapeutic measure is available, the early diagnosis has become more urgent. Physiologically, the patient has a stenosis of the aorta distal to the left subclavian artery In consequence, due to this impedance of heart output, there occurs a hypertension in the fore quarters of the body This hypertension may frequently be of the order of 170 to 180 systolic over 90 to 100 diastolic The increased head of pressure in the fore-quarters and the low pressure in the hind quarters encourages the development of large, dilated collateral circulation, the intercostal arteries, the internal mammary artery and the scapula arteries become very dilated. Although enough blood will get through the collateral circulation to maintain the nutrition and function of the hind-quarters, the head of pressure will be low and femoral artery pulsations will be weakened or absent. Thus, the diagnosis can usually be made by recording hypertension in the fore-quarters and hypotension in the hind-quarters The maintenance of this hypertension in the fore-quarters will carry with it all the possible sequelae of hypertension, left ventricular failure may supervene, arteriosclerosis of the vessels carrying an increased head of pressure may occur and vascular accidents in the cerebral vessels are not infrequent The dilated intercostal arteries usually erode the inferior edge of the ribs, but this does not usually occur before the age of ten and the upper three or four and lower three or four ribs are likely to be spared There may



FIG 8 X-ray film of the chest in an uncomplicated patent ductus arteriosus later corrected surgically Fullness of the pulmonary arteries is the conspicuous feature

the dynamics are upset, there *is no cyanosis* (Figures 7 and 8) It is the consensus of surgical opinion that these shunts should be closed before any damage to the vascular system or complications develop The usual procedure is to advise closure of the shunt in the age group, five to eight years If cardiac failure supervenes before this age, operation sooner is in order In most surgeons' hands the operation has a very low operative mortality rate, though rarely the patient will expire on the operating table after the chest is opened before anything is done to the ductus This probably results from cardiac failure during the stress and strains of anesthesia and surgery Cardiac catheterization is

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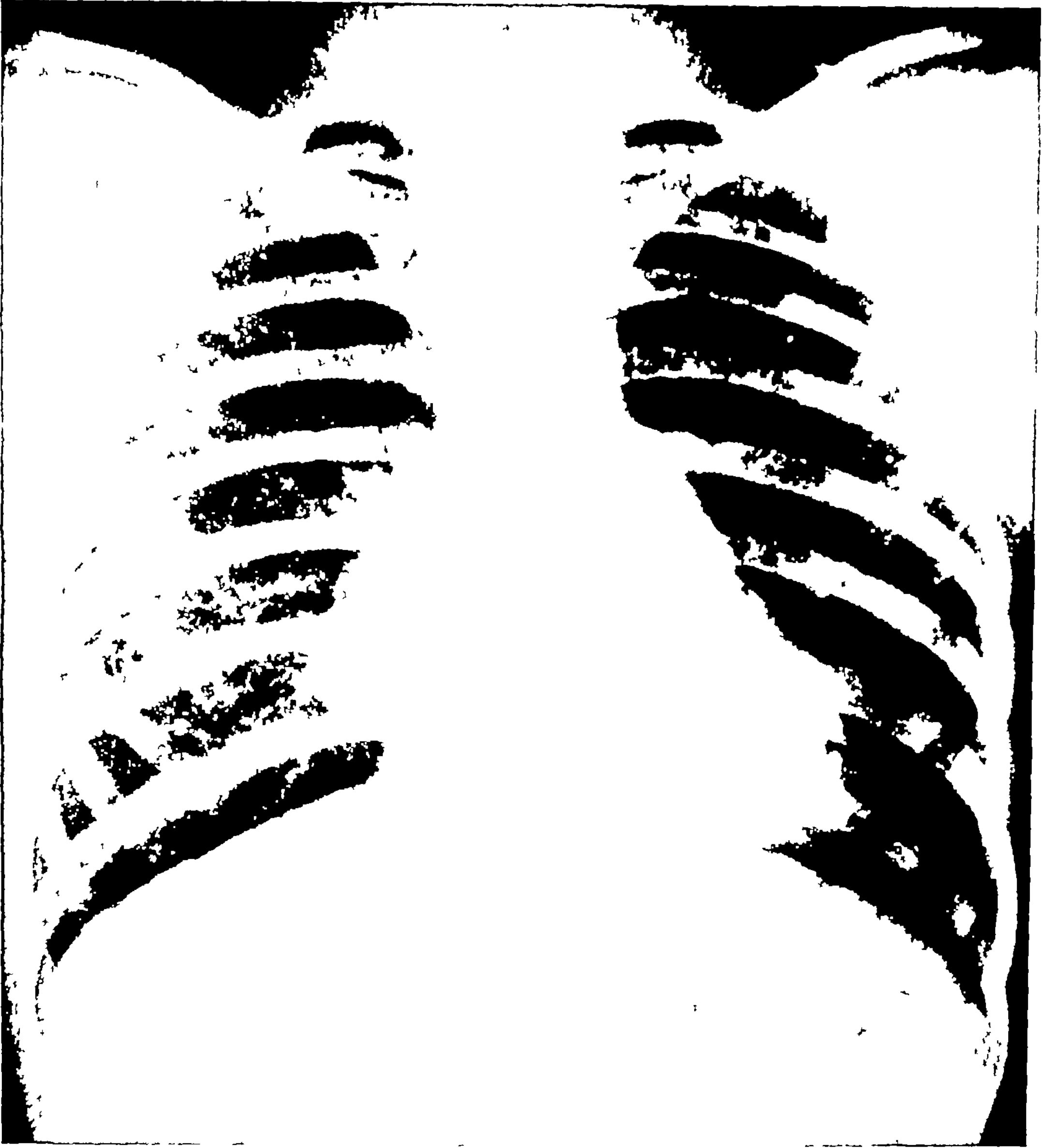


FIG 8 X-ray film of the chest in an uncomplicated patent ductus arteriosus later corrected surgically Fullness of the pulmonary arteries is the conspicuous feature

the dynamics are upset, there *is no cyanosis* (Figures 7 and 8) It is the consensus of surgical opinion that these shunts should be closed before any damage to the vascular system or complications develop The usual procedure is to advise closure of the shunt in the age group, five to eight years If cardiac failure supervenes before this age, operation sooner is in order In most surgeons' hands the operation has a very low operative mortality rate, though rarely the patient will expire on the operating table after the chest is opened before anything is done to the ductus This probably results from cardiac failure during the stress and strains of anesthesia and surgery Cardiac catheterization is

usually not necessary unless the ductus is thought to be complicated by some other defect In the "pure" ductus the admixture of oxygenated blood in the pulmonary artery and the elevated pulmonary artery pressure will be diagnostic

Coarctation of the Aorta is of two types, the infantile and the adult type The infantile type was so named because it was felt that infants with the lesion seldom lived to adult life In the usual infantile lesion, the stenosis is close to the left subclavian artery and is more difficult to treat than the adult type, for the adjacent subclavian artery (the chief collateral) may have to be clamped The more usual type of coarctation of the aorta, the adult type, consists of a stenosis, partial or complete, about one to two centimeters long, occurring just distal, to the left subclavian artery at the point the patent ductus arteriosus takes off from the aorta (Figure 9) However, there is overlapping in these two categories and combinations of the two occur

It has been estimated by Levine from autopsy figures that one out of every thousand persons has some degree of coarctation of the aorta Only the patients with a serious degree of stenosis will present themselves for treatment In the past, the disease has been missed all too often Now that a therapeutic measure is available, the early diagnosis has become more urgent Physiologically, the patient has a stenosis of the aorta distal to the left subclavian artery In consequence, due to this impedance of heart output, there occurs a hypertension in the fore quarters of the body This hypertension may frequently be of the order of 170 to 180 systolic over 90 to 100 diastolic. The increased head of pressure in the fore-quarters and the low pressure in the hind quarters encourages the development of large, dilated collateral circulation, the intercostal arteries, the internal mammary artery and the scapula arteries become very dilated. Although enough blood will get through the collateral circulation to maintain the nutrition and function of the hind-quarters, the head of pressure will be low and femoral artery pulsations will be weakened or absent. Thus, the diagnosis can usually be made by recording hypertension in the fore-quarters and hypotension in the hind-quarters The maintenance of this hypertension in the fore-quarters will carry with it all the possible sequelae of hypertension, left ventricular failure may supervene, arteriosclerosis of the vessels carrying an increased head of pressure may occur and vascular accidents in the cerebral vessels are not infrequent The dilated intercostal arteries usually erode the inferior edge of the ribs, but this does not usually occur before the age of ten and the upper three or four and lower three or four ribs are likely to be spared There may



FIG 9(a) Angiocardiogram view of coarctation of the aorta, shown above

be heard a systolic murmur over the precordium, and bruits over the dilated vessels are not infrequent

After the surgical correction of this condition, which consists in freeing up the aorta, removing the stenosed section and restoring continuity, there should be an essentially normal cardiovascular system Gross has pointed out that after doing an anastomosis, care must be taken to open the clamps on the aorta slowly, so that the blood volume

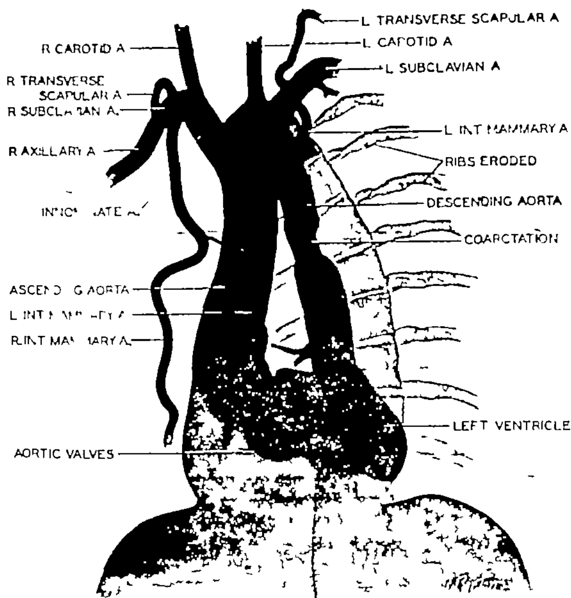


FIG 9(b) Is a sketch of the findings. It shows less stenosis than usual Note the dilated collateral arteries and the notching under the ribs. (Courtesy Dr Sol Katz.)

and blood vascular system can readjust to each other It is conceivable that with the blood vessels of the hind-quarter maximumly dilated and the sudden opening of the clamps, the patient may literally "bleed to death in his own blood vessels" However, with the use of blood transfusions and the slow opening of the clamp, this should be obviated In all these types of vascular surgery, the liberal use of whole blood when needed has proved to be life-saving and, more recently, it has been proposed that the blood be given intra arterially so that it may be replaced more quickly and more safely with less danger of overloading the pulmonary circulation at a time when the myocardium may be

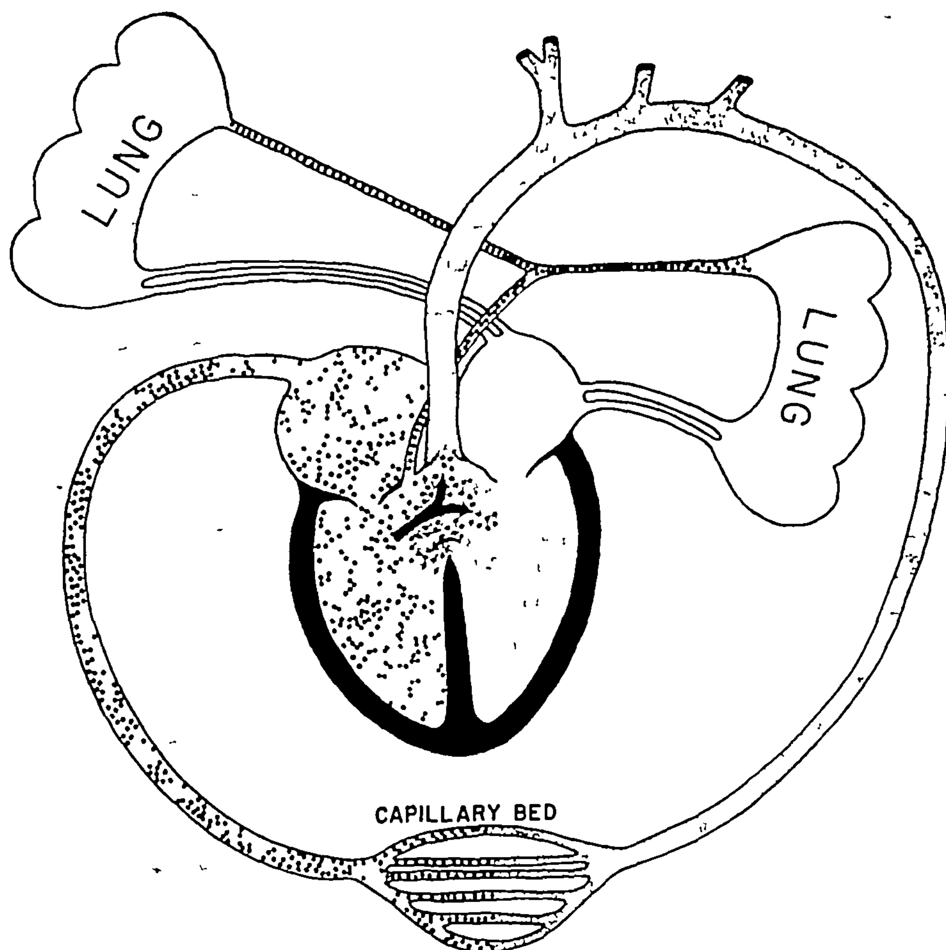


FIG 10 Diagram of the circulation as found in Tetralogy of Fallot

ischemic due to low systemic pressure In some cases the stenosis of the aorta may be too long to permit a primary end to end anastomosis of the aorta Also at times the distal segment of the aorta may be sufficiently thin and there may be a sufficient degree of atherosclerosis that a primary end to end anastomosis of the aorta might be dangerous In these instances, Gross has introduced the method of grafting a piece of aorta from a cadaver This has been successfully done in numerous instances The donor aortas are usually collected four to six hours after death using sterile precautions and stored in Hanks solution The graft can then be kept at four degrees centigrade for as long as a month and by tissue culture studies will remain viable However, the ultimate fate of these grafts in the body as time goes on is not yet known, and it seems reasonable that whenever possible, a primary end to end anastomosis should be done rather than using a graft,

There exists a considerable number of cases who have congenital heart disease which causes cyanosis The majority of these patients will

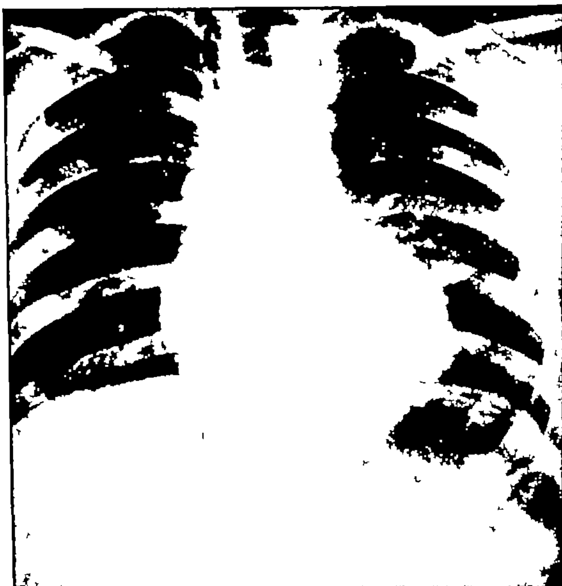


FIG. 11 X ray film taken from a patient with Fallot's Tetralogy Diminution in size of the pulmonary arteries and enlargement of the right ventricle are the conspicuous features here

have a syndrome known as the *tetralogy of Fallot* The tetralogy of Fallot consists primarily in pulmonary stenosis, which usually occurs in the neighborhood of the pulmonary valve Associated with this there is an over riding of the aorta, an intraventricular septal defect and a dilatation and hypertrophy of the right ventricle With the stenosis of the pulmonary valve which impedes the outflow of blood from the right ventricle and with the presence of an intraventricular septal defect the bulk of the blood ejected by the right ventricle will pass directly into the left ventricle This constitutes a right to left shunt, and consequently the patient will suffer from cyanosis which may vary from slight to severe depending upon the amount of blood that has shunted across

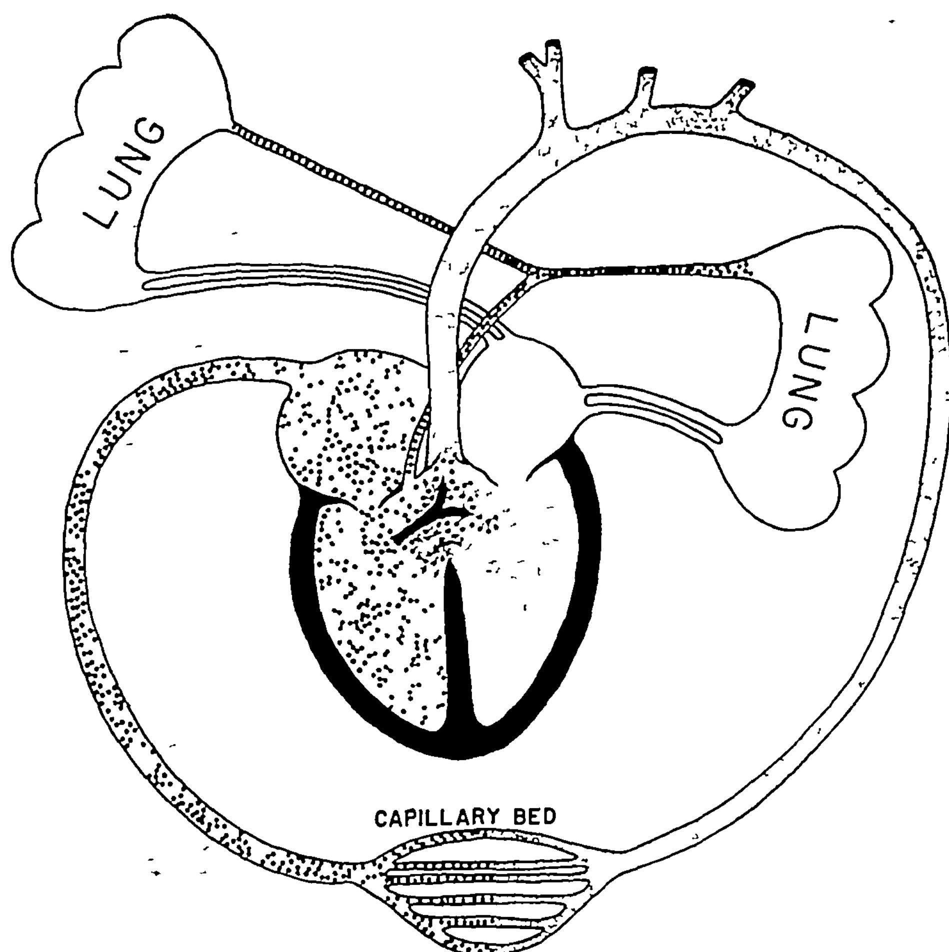


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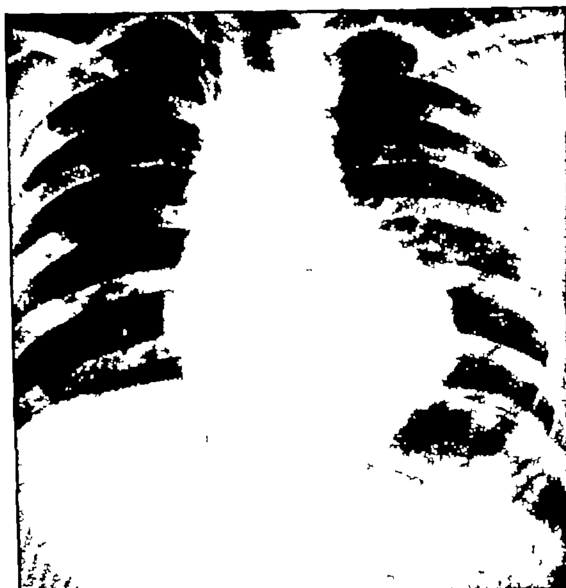


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(Figures 10 and 11) Because of the stenosis of the pulmonary artery, there will be a reduced amount of blood flowing through the lungs to be oxygenated. The pulmonary artery pressure is lower than normal One patient, for example, was found to have ten millimeters of mercury systolic and seven millimeters of mercury diastolic pressure. The systemic blood flow will be within normal limits There is extra strain on the right ventricle which must beat against a much higher pressure than normal There is compensation on the part of the body itself to adapt itself to this lower arterial tension of oxygen, and polycythemia is common This may vary from slight to severe degree with hematocrits on record as high as 80. The blood is sirupy in character and is very prone to clot Consequently, thromboses throughout the body are frequent sequelae of severe degrees of pulmonary stenosis in tetralogy of Fallot

Clinically these children are found to be cyanotic, the cyanosis worsens with exercise and the subject usually prefers to squat while recovering This act of squatting apparently aids in elevating the cardiac output, which helps the oxygen delivery to the tissues The patients usually have a systolic murmur heard over the precordium In a roentgen view of the chest, there will be diminished pulmonary artery markings and right ventricular enlargement At operation the pressures measured in the pulmonary arteries will be much lower than normal, may often be under 10 millimeters of mercury pressure There are various types of this disease in that the pulmonary arteries may be at times non-existent There is usually an associated dextra-aorta in about 20 per cent of the cases Taussig, Bing, Dexter, Cournand have all studied these cases medically Cardiac catheterization is not necessary in most cases, but some cases may present vascular problems, which can only be accurately diagnosed by means of catheterization studies Often the catheter is introduced more readily into the left ventricle than into the pulmonary artery

The consensus at present is that patients suffering from tetralogy of Fallot, if they have reduced arterial oxygen saturations below 85 per cent at rest and if they have incapacitating symptoms, would benefit by the creation of a left to right shunt to add systemic artery blood to the lungs This is usually advocated in the four to eight year age group, though if the patient is in a desperate situation, this may be done sooner and of course later The procedure introduced by Blalock consists in taking a systemic artery, usually the subclavian, on the side away from the descending aorta and anastomosing the end of this vessel into the side of the pulmonary artery The Potts' modification of

this procedure advocates the creation of an artificial patent ductus by doing a direct side to side anastomosis between the descending aorta and the adjacent pulmonary artery This has the advantage of permitting the construction of any size shunt desired but has the disadvantage that the size of the shunt must be very carefully controlled for fear that too much blood may flow to the lungs through too large a shunt, with adverse effects on the heart With a right aorta the Potts operation is less favorable It is possible through one of these operations to give marked relief to some of the subjects, for example, an arterial oxygen saturation of 60 per cent may be raised up into the 80 per cent range

Brock has emphasized that the pulmonary stenosis in tetralogy of Fallot is usually a stenosis in the infundibulum below the pulmonary valve He has successfully enlarged the stenosed infundibulum by means of a valvulotome passed through the wall of the right ventricle In uncomplicated pulmonary stenosis the pulmonary valve itself is usually affected Brock has corrected this too with a valvulotome

The Brock operation has the advantage of correcting an abnormal situation, while the Blalock procedure relieves an abnormal situation by another abnormality More time must elapse to evaluate these methods properly The study of this field by Blalock and Taussig has been a brilliant contribution

There exists a condition known as *Eisenmenger's syndrome* where the situation is apparently like tetralogy of Fallot, except that there is no pulmonic stenosis The stenosis apparently is in the blood vascular system in the lung parenchyma The patient is cyanotic and has an elevated pulmonary artery pressure Bing reported one patient with a pulmonary artery pressure of 122 systolic, 86 diastolic, and 98 mean (millimeters of mercury) The creation of a systemic pulmonary shunt in such a condition will serve no useful purpose.

Tricuspid Stenosis This type lesion usually is associated with an interauricular septal defect The tricuspid valve is stenosed, the right ventricle is atrophic These patients have right to left shunts, and they are cyanotic Surgical creation of an artificial shunt to carry more systemic blood to the lungs is palliative The tricuspid valve has not been attacked directly because of the accompanying ventricular atresia

Anomalies of the vessels may also cause obstructive symptoms *A double aortic arch* encircles the trachea and esophagus One arch obstructs the trachea in front the other arch obstructs the esophagus from behind The diagnosis can be suspected in an infant with cyanosis and some dysphagia Sectioning of the aortic arch can be life-saving

Rarely an *anomalous right subclavian artery* arises from the aortic

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Analysis by Maude Abbott of 402 auricular septal defects revealed 290 patients with a patent foramen ovale, 36 cases of persistent ostium primum, 19 cases of persistent ostium secundum, 28 multiple defects of the septum, 14 instances of complete absence of the septum in a bilocu late heart and 15 instances of complete absence of the auricular septum in a triloculate heart Most instances of patent foramen ovale are of no clinical significance Only about 15 per cent of Maude Abbott's cases of patent foramen ovales were pure patency A small slit is of no im portance A moderate opening is significant only when the right auricu lar pressure is increased over the left auricular pressure, and a right to left shunt occurs with cyanosis

The defects are significant if a large area of the septum is involved (White) The lesions that seem most amenable to surgery are the de fects in the lower part of the septum, caused by primitive ostium primum and the lesions in the upper part of the septum, caused by primitive ostium secundum The situations where the septum is en tirely lacking would be much more difficult to correct

The defect in the auricular septum permits blood to flow from the left to the right auricle There is no cyanosis unless the flow is reversed Catheterization studies have shown auricular pressure readings of zero to five millimeters of mercury in the right auricle and minus five to plus 15 millimeters of mercury in the left auricle The mean pressure in the left auricle has been found to be about two to four milli meters of mercury higher than in the right auricle The left to right shunt increased the work of the right side of the heart. The right ven tricular output and pressure are elevated The pulmonary artery pressure is increased, the artery is dilated The electrocardiograph shows right axis deviation Although patients with auricular septal defects may live long and normal lives, enlargement and failure of the right ventricle are common Paradoxical embolism through the shunt is possible The actual pressures can be measured with the cardiac catheter, and the admixture of oxygenated blood in the auricle will be diagnostic of the condition The catheter can be introduced into the left side of the heart The possible amount of blood flowing through the shunt can be calculated (see catheterization calculations later in this chapter)

An interesting syndrome with an auricular septal defect is *Lutem bacher's syndrome* In this condition mitral stenosis exists together with an auricular septal defect The septal defect relieves the pulmonary engorgement which would ordinarily result from the mitral stenosis If the septal defect were closed and the mitral stenosis were not re-

arch distal to the left subclavian The anomalous vessel passes behind the esophagus, obstructs it, and causes symptoms from esophageal obstruction The symptoms can be relieved by sectioning the anomalous artery

Intrapulmonary Arteriovenous Fistula: Intrapulmonary arteriovenous fistulae have been described in the lung The concentration of interest on thoracic problems will, no doubt, find many more of these abnormalities They may be caused by trauma, infection or regenerative changes, but apparently a considerable number are congenital, probably progressive, probably familial and often multiple Too few of these patients have been subjected to intensive physiological study to draw any conclusions concerning the effect of a shunt in the lesser circulation Maier *et al* reporting studies on one patient with an infected shunt treated by resection, found an arterial oxygen saturation of 74 per cent at rest, and 59 per cent after exercise The right ventricular pressure was 17 millimeters of mercury systolic and eight millimeters of mercury diastolic The cardiac output was normal It was calculated that 58 per cent of the right ventricular output went through the fistula The hematocrit was 70 per cent in this instance It is impossible, so far, to measure the venous pressure in the lesser circulation in the intact patient

Thus an intrapulmonary arteriovenous fistula in effect is a right to left shunt It permits venous blood to enter the greater circulation Polycythemia and cyanosis proportional to the shunt will result This one case suggests that the cardiac output is not increased in contrast to what is found in an arteriovenous shunt of the systemic circulation

Anomalous Pulmonary Vein: Thoracic surgeons have often noted abnormal pulmonary vessels while operating in the thorax Probably a rare, but perhaps an important condition exists wherein a pulmonary vein empties directly into a systemic vein, instead of into the right auricle This permits oxygenated blood to enter a systemic vein and re-enter the right ventricle The effect of this circus movement of blood through the pulmonary circulation was studied in at least one instance by Cooke and Evans Their data are as yet unpublished

It would seem reasonable to suggest that this abnormal communication should be closed surgically if signs of right ventricular strain should develop

Interauricular Septal Defects: Interauricular septal defects are the commonest congenital cardiovascular defect At the present time there is no satisfactory method of closing these defects in man In the near future this problem will be solved surgically

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The estimated pulmonary blood flow must be considered in two different cases In the first case the pulmonary artery flow is the same as the pulmonary capillary flow This means that no systemic blood is shunted to the pulmonary circulation distal to the point of sampling Then the pulmonary artery flow equals the oxygen consumption divided by (the oxygen saturation in the left auricle minus the oxygen saturation in the pulmonary artery) In the second case it is suspected that the aortic system supplies blood to the pulmonary circulation distal to the point of sampling in the pulmonary system Here the pulmonary flow cannot be accurately measured However, it will be greater than the pulmonary artery flow as calculated above but less than if all the blood were supplied by the aortic system The aortic system flow would thus equal oxygen consumption divided by (oxygen saturation to the left auricle minus the oxygen saturation of the aorta)

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Note that the formula for each of these shunts is the systemic blood flow multiplied by the increment of saturation in the main flow divided by the decrement in saturation in the direction of the shunt.

The first three types were examples of single shunts At times there

lieved, the patient would be made worse In fact, some of the surgical attacks on mitral stenosis have been aimed at producing an artificial Lutembacher's syndrome

Interventricular Septal Defects· Interventricular septal defects are the second commonest congenital cardiovascular defect Murray has passed fascia lata sutures anteriorly and posteriorly through the septum and closed or partially closed the defect Careful attention to anatomical details is imperative to avoid damaging the coronary blood supply However, the fully satisfactory surgical treatment of this lesion will probably not be available until the defects can be closed under direct vision

The great majority of these lesions are complicated by other defects Only about 25 per cent of Maude Abbott's cases were not associated with other lesions Nearly 95 per cent of the defects occurred at the base of the heart just below the aortic valve The defect is usually small, oval or circular and one to two centimeters in diameter (White) Since left ventricular pressure is normally greater than in the right ventricle, the shunt is left to right and there is no *cyanosis* The right ventricle has higher pressure than normal and has extra work to do The pulmonary artery is slightly dilated The cardiac catheter can detect the admixture of oxygenated blood in the right ventricle and a higher than normal pressure At times the catheter can be passed into the left side of the heart The volume of blood passing through the shunt can be calculated (see catheterization calculations in this chapter) An uncomplicated ventricular septal defect has been named *Roger's Disease* Patients with the uncomplicated ventricular septal defects may live long, normal lives However, the average life span is markedly shortened The longest survival in Maude Abbott's series was 49 years Gelfman and Levine reporter a high incidence of 57 per cent subacute bacterial endocarditis in patients with ventricular septal defects Certainly the surgical closure of this defect in Roger's Disease would be desirable

Cardiac Catheterization in Congenital Cardiovascular Disease· Normally the catheter is introduced through a systemic vein into the right auricle, right ventricle, pulmonary truncus, and left and right pulmonary arteries If a septal defect be present, the catheter can be introduced into the systemic circulation Pressure measurements are also taken The systemic blood flow, the left ventricle output, the pulmonary blood flow and the right ventricle output will all be approximately equal in a normal situation The estimation of the systemic blood flow by the direct Fick method has already been described under nor-

mal cardiac output The blood carried by a shunt can be estimated if certain data are known (Cournand)

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may be more than one shunt For example, the saturation in the right ventricle may be greater than the saturation in the right auricle, and the saturation in the pulmonary artery may be greater than the saturation in the right ventricle The formulae to calculate these shunts become quite complex depending upon the clinical entity suspected 4 The reader is referred to a specialized reference such as Cournand's Monograph 5 In this situation the arterial blood saturation is below its normal value of 96 per cent, and thus a right to left shunt is suspected The shunt equals the *systemic flow* times (the *left auricle saturation* minus the *aortic saturation*) divided by (the *left auricle saturation* minus the *vena caval saturation*)

Acquired Cardiovascular Disease · Most of the surgical attention has been focused on congenital defects Actually the acquired defects far outnumber the congenital defects

Surgery for coronary artery disease has already been described The surgery of *traumatic lesions* such as stab wounds produce physiological changes mainly by cardiac tamponade

Foreign bodies in the heart and great vessels may cause physiological changes by obstruction, aneurysm formation, myocardial rupture or thrombus formation Harken removed foreign bodies from the heart (all chambers) and great vessels in 134 instances with no operative deaths

Surgery for *aneurysms of the aorta* has been done The main approach has been to reinforce the weakened vessel by wrapping fibrosing type cellophane around the aneurysm or by promoting clot within the vessel, e g , steel wire In most instances these results have been disappointing Perhaps blood vessel grafts, in the traumatic cases at least, will improve the results Aneurysms of other vessels will be described in the next chapter

Recently, experimentally produced *myocardial infarcts* have been excised in dogs with surprisingly high rates of survival What new surgical application this may have is not yet known Intracardiac *valve cusp replacements* have been done experimentally but their application to humans will, no doubt, have to wait for the development of a satisfactory mechanical pump to substitute for the heart temporarily

Of the acquired cardiovascular defects, mitral stenosis has received most of the recent surgical attention

Surgery for Mitral Stenosis In mitral stenosis there is impairment of diastolic filling in the left ventricle and regurgitation of blood from the left ventricle into the left auricle during systole As has already been described, the auricle and pulmonary veins are dilated The pres-

sure in the pulmonary veins may be 500 millimeters of water Lowered left ventricular output and acute pulmonary edema occur For years the surgical world has sought a method of therapy One possibility is to shunt blood around the stenosed mitral valve Another way is to decompress the pulmonary veins, and a third approach is to enlarge the opening in the mitral valve

Efforts to create a shunt around the mitral valve by experimentally anastomosing grafts from the left auricle to the left ventricle, by creating shunts from the pulmonary veins to systemic arteries, and many others have been impractical Sweet has anastomosed a pulmonary vein to the azygos vein This seems to help the pulmonary edema in some patients, but it will not raise the cardiac output of the patient who has a fixed low cardiac output

The direct attack on the valve has been attempted many times in the past Most attempts consisted of removing a segment of the stenosed valve The enlarged opening permitted more diastolic filling, but it also caused more regurgitation The mortality rate precluded popularization of this operation Most of the attacks on the valve have been by way of the left auricle Smithy advocated approach to the valve through the ventricle and showed that novocaine injected into the myocardium would protect against arrythmias Harken and Bailey have contributed to this field of valvulotomy for mitral stenosis Bailey introduced the concept of commissurotomy for mitral stenosis Commissurotomy makes use of the fact that if the two fused cusps be cut along their line of fusion to each other, the stenosis will be opened, but the cusp will regain some function and less regurgitation will occur than if a piece of valve were removed The long range evaluation of this method has yet to be obtained The introduction of a successful cardiac pump to permit direct view valvulotomy will someday modify the operation for mitral stenosis

Aneurysm of the Pulmonary Artery Aneurysms of the pulmonary artery are, no doubt, rare lesions Most of the literature concerns anatomical findings at autopsy They are being found now that surgeons explore abnormal x ray shadows in the pulmonary hilum. These aneurysms frequently rupture and cause sudden death in 35 per cent of the cases The average duration before rupture is about five years It has been known for years that the pulmonary artery could be ligated and the lung left in place The lung loses its ability to respire but will continue to ventilate Lung function studies by Humphreys showed no oxygen uptake in the lung with its pulmonary artery ligated, but some carbon dioxide excretion occurred Pulmonary artery pressures and

may be more than one shunt For example, the saturation in the right ventricle may be greater than the saturation in the right auricle, and the saturation in the pulmonary artery may be greater than the saturation in the right ventricle The formulae to calculate these shunts become quite complex depending upon the clinical entity suspected 4 The reader is referred to a specialized reference such as Cournand's Monograph 5 In this situation the arterial blood saturation is below its normal value of 96 per cent, and thus a right to left shunt is suspected The shunt equals the *systemic flow* times (the *left auricle saturation* minus the *aortic saturation*) divided by (the *left auricle saturation* minus the *vena caval saturation*)

Acquired Cardiovascular Disease Most of the surgical attention has been focused on congenital defects Actually the acquired defects far outnumber the congenital defects

Surgery for coronary artery disease has already been described The surgery of *traumatic lesions* such as stab wounds produce physiological changes mainly by cardiac tamponade

Foreign bodies in the heart and great vessels may cause physiological changes by obstruction, aneurysm formation, myocardial rupture or thrombus formation Harken removed foreign bodies from the heart (all chambers) and great vessels in 134 instances with no operative deaths

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Chapter III

BLOOD VESSELS

Resistance The arterioles provide most of the peripheral resistance to blood flow At the root of the aorta the total caliber of the channel through which all the blood must flow is identical with the caliber of the aorta itself At the level of the arterioles the total vascular bed is much greater than it is in the larger arteries (Figure 12) The multiplicity of vessels of fine caliber splits up the blood stream and presents a larger surface area on which forces of friction and viscosity come into play

Capillaries are much narrower than arterioles, and yet the resistance in the capillaries is far less than in the arterioles The cross-section area of the capillary bed is enormously greater than the cross section area of the arteriole bed The capillary increase in area overshadows the decrease in caliber of the individual vessels

The venules offer less resistance than the capillaries The cross section area of the veins decreases as the heart is approached, but the individual veins become larger and larger in caliber nearer the heart The increase in caliber reduces the factors of friction and viscosity to a minimum

Pressure At the beginning of the large arteries the blood has a mean pressure of about 100 millimeters of mercury There is a moderate decrease in pressure as the blood passes through the larger arteries When entering the arterioles, the blood has a mean pressure of approximately 70 millimeters of mercury

The greatest fall in blood pressure occurs while the blood is passing through the arterioles The pressure falls from about 70 millimeters of mercury to approximately 30 millimeters of mercury The precise level of blood pressure in the capillaries in man can only be approximated Landis studied capillary pressures in the skin of the hand in man He found that the arteriolar end of the capillary loop had a pressure in the range of 28 to 65 centimeters of water The pressure in the top of the loop was 20 to 43 centimeters of water The venous limb of the capillary loop contained blood under a pressure of 8 to 24 centimeters of water If blood enters the capillaries with a pressure of 30 millimeters of mercury it leaves them with a pressure of 10 millimeters of mercury

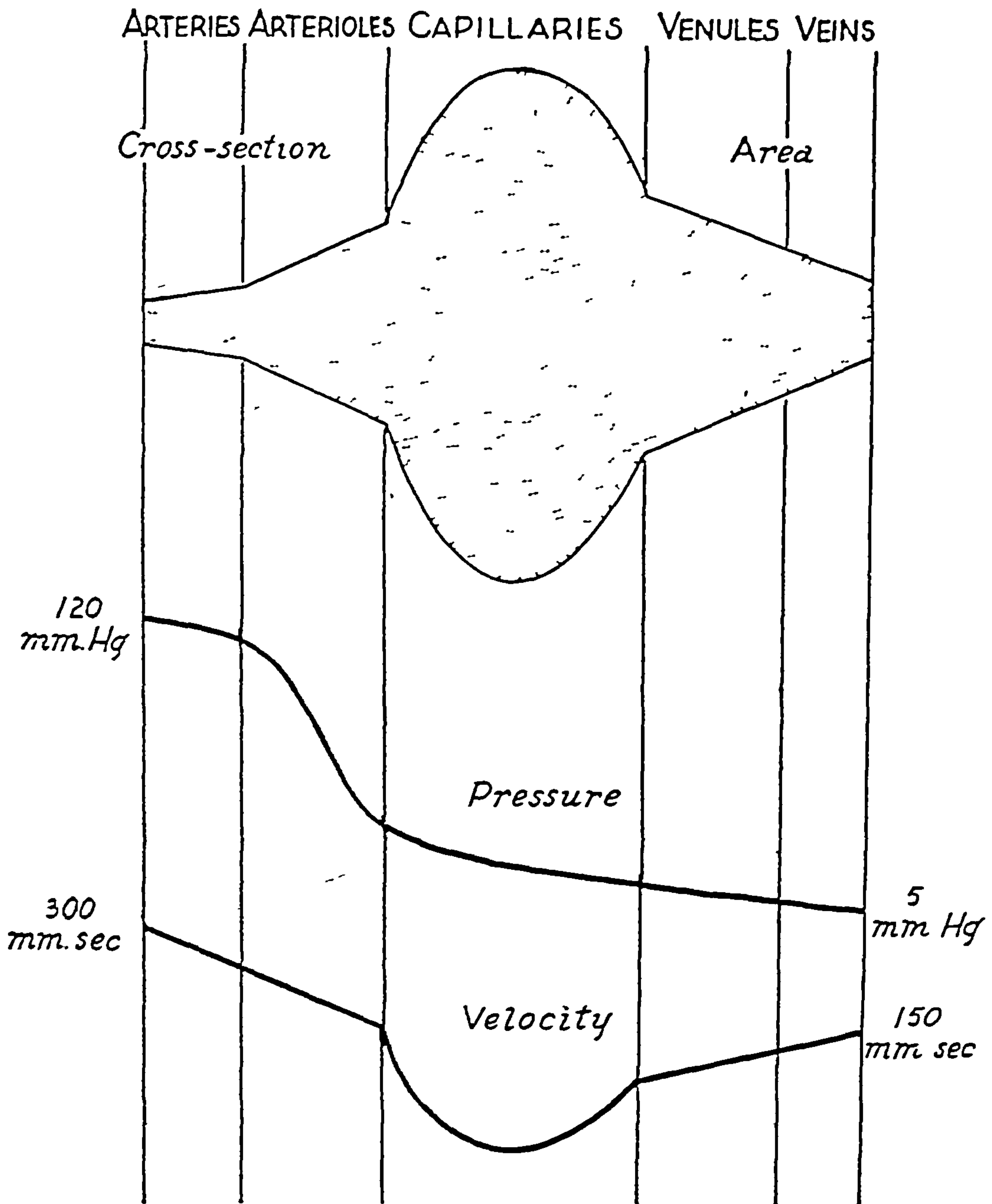


FIG 12 Diagram indicating total cross-section area, blood pressure, and linear velocity of blood flow in the different parts of the vascular system.

The fall in pressure is least in the veins Blood enters the veins with about 10 millimeters of mercury pressure and leaves the great veins to enter the heart with approximately 2 millimeters of mercury pressure.

From the great arteries to the heart there is a steady decrement in blood pressure If this were not so there would be a reversal of flow back to the left side of the heart The pressure in the great veins approaches zero. The actual level of pressure is determined by the posi-

tion of the patient and the reference point from which the measurement is made. Usually the level of the right auricle serves as a base line in measuring venous pressure The venous pressure varies with the phase of respiration and at times may become relatively negative

Control of the Arterioles The peripheral resistance in the arterioles is not only larger than in any other group of vessels, but it is also the most adjustable The smooth muscle in the walls of the arterioles can alter the caliber of the vessels in accordance with physiological needs The arterioles can be controlled by both nervous influences and chemical factors

Nervous Control The vasomotor system supplies the nervous control of the arterioles This system is the most important single factor in the control of peripheral resistance It is dominated by a center in the medulla which is chiefly a vasoconstrictor center The existence of a vasodilator center is questionable Dilation of the arterioles is achieved mainly through inhibition of the vasoconstrictor center The vasomotor center receives afferent impulses from all parts of the body, but it is influenced particularly by certain reflexes which also control the heart. Some of these latter reflexes are the depressor reflex from the aorta and carotid sinus and the Bainbridge reflex from the right auricle

Chemical Control The arterioles can be controlled chemically by substances which cause either constriction or dilatation through effects on the vasomotor center in the medulla or on the arteriolar wall itself

The hydrogen ion concentration of the blood acts centrally (vasomotor center) and peripherally (arteriolar wall) Increase in the hydrogen ion concentration stimulates the vasomotor center, causing generalized vasoconstriction and a rise in blood pressure Increased hydrogen ion concentration acting peripherally on the wall of the arteriole causes dilatation of the vessel The central effect is stronger When the acidity of the circulating blood increases, the central vasoconstriction predominates over peripheral vasodilatation, and the blood pressure rises

The physiology of muscular exercise illustrates the harmonious cooperation of the contrary effects of the hydrogen ion concentration Active muscles liberate acidic products which are carried to the vasomotor center in the medulla and bring about an increase in blood pressure This is desirable The hydrogen ion concentration rises highest in the active tissues The high local concentration by direct action on the arterioles in the neighborhood causes local vasodilatation and an increase in blood flow through the active tissue.

Increase of carbon dioxide in the blood causes increased hydrogen

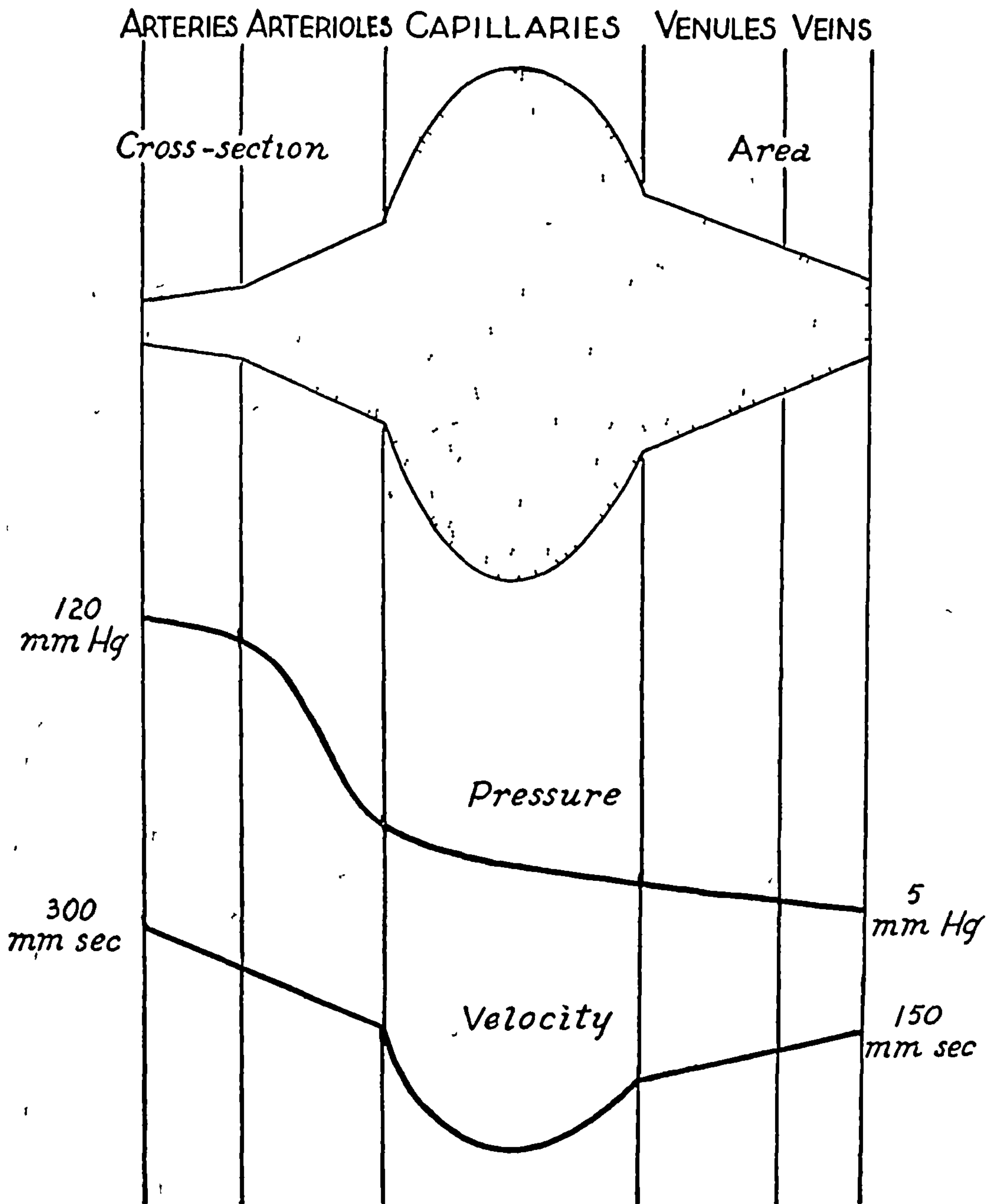


FIG 12 Diagram indicating total cross-section area, blood pressure, and linear velocity of blood flow, in the different parts of the vascular system

The fall in pressure is least in the veins Blood enters the veins with about 10 millimeters of mercury pressure and leaves the great veins to enter the heart with approximately 2 millimeters of mercury pressure

From the great arteries to the heart there is a steady decrement in blood pressure If this were not so, there would be a reversal of flow back to the left side of the heart The pressure in the great veins approaches zero The actual level of pressure is determined by the posi-

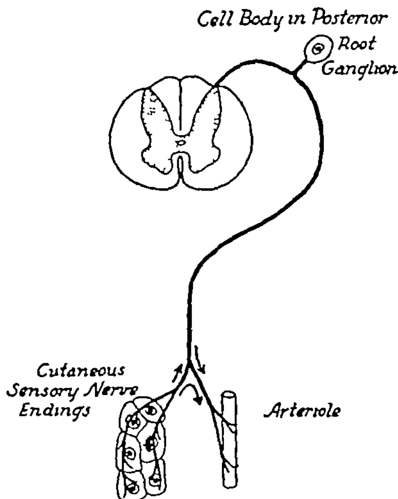


FIG. 13 Diagram of axon reflex arc.

There is no satisfactory evidence that pituitrin is responsible for the maintenance of normal capillary tone

Dilatation of the capillaries is produced when there is increased hydrogen ion concentration in the fluid bathing their walls Dilatation of the arterioles in the same manner has already been mentioned It is physiologically useful to have the capillaries and arterioles of active tissues dilate while there is vasoconstriction and a general rise in blood pressure elsewhere

Triple Response Lewis found that a characteristic local vascular reaction follows any type of stimulation—mechanical, electrical, thermal, chemical, photochemical or toxic—by which cells are mildly injured The full response of normal skin, called by some "the Triple Response consists of (1) active local dilatation of minute vessels, including capillaries, (2) a spreading flare due to active dilatation of neighboring arterioles, and (3) the formation of a pale, elevated wheal The vascular response to trauma occurs in systemic as well as cutaneous areas It has been demonstrated in the visceral organs It cannot be

ion concentration. This mechanism explains the marked rise of blood pressure in asphyxia.

Control of the Capillaries: The capillary bed offers little resistance to the circulating blood, but there is a certain resistance maintained by the tone of the vessels. This tone is essential for normal circulation, for if the entire capillary bed were to dilate, there would not be enough blood to fill the cardiovascular system. The capillary endothelial wall itself has the power of independent contractility to a certain degree. The Rouget cells which encircle some capillaries at intervals act like smooth muscle cells in altering the caliber of the vessels. The endothelial wall and the Rouget cells are the principal means of maintaining capillary tone. These two mechanisms are under chemical and nervous controls.

Nervous Control. The axon reflex arc is one means of local nervous control. An axon reflex arc consists of a cerebrospinal nerve fiber (not an autonomic) with two branches. One branch ends in a sense organ, while the other terminates in contact with the wall of a nearby capillary. Stimulation of the sense organ causes an afferent impulse to reach the central nervous system and to give rise to subjective perception (sensation) of the stimulus. Since the impulse spreads through all parts of the nerve cell and its processes, it passes down the axon branch which ends at the capillary (Figure 13). The impulse thus causes dilatation of the capillary. The axon reflex occurs even if the nerve fiber has been divided above the point of branching. It is believed that counterirritants applied locally cause their vasodilating effects chiefly through the axon reflex.

A more widespread nervous control is effected through automatic vasomotor fibers which pass from the spinal cord to the capillaries, exactly like those which control the arterioles. This central capillary nervous control seems to be weak and is relatively unimportant. Its very existence was not generally accepted until recently. There is no known medullary center for the unified control of the capillaries.

Chemical Control. The chemical control of the capillaries seems to be more important than the nervous control. Chemical control is not well understood. Adrenalin can cause either constriction or dilatation of capillaries according to its concentration. It is believed that adrenalin has practically no influence on capillary tone in the concentrations which occur in the blood under ordinary conditions. The vascular effects of adrenalin which are maintained are restricted to the arterioles. Pituitrin may cause capillary constriction or dilatation experimentally but has no noteworthy effect under clinical conditions.

Valves of the Veins The valves in veins play a basic role in producing adequate venous return According to Franklin, the valvular cycle is as follows Muscular contraction forces blood toward the heart by compressing the vessel This produces a rise in venous pressure proximal to the constriction which closes the valve If the flow of blood from the capillaries has reestablished the gradient, the valve opens even if the muscle is still contracting As a result of this mechanism, venous blood is kept flowing toward the heart.

Effects of Posture The effect of posture on the blood flow was studied by Thompson and others who found that in the standing position the blood above the level of the heart may circulate two or three times as rapidly as that mounting up from the lower extremities. Increase in the volume of the lower extremities occurs on standing, due to distention of the veins and increased filtration of fluid into the spaces as a result of the elevated capillary pressure.

Factors counteracting the vascular pooling effect of gravity are peripheral vasoconstriction, acceleration of the heart, heightened tonus of the skeletal muscles, and closing of the vein valves

Varicose Veins Varicose veins may be defined as abnormally dilated veins with degenerative structural changes in the vein walls For practical purposes the lower extremity varicosities are the most important.

An increase in venous pressure within the varicose system has been demonstrated by many investigators The pressure is not always increased in primary varicose veins, but in secondary varices pressures may reach high levels Ochsner and Mahorner have shown that even in primary varicose veins in the erect position, venous pressure may rise to 1200 millimeters of water

Of more importance than pressure changes is the marked change in the venous blood flow This is particularly true of the saphenous system in which the blood flow may become retrograde in the erect position The relationship between the superficial and deep circulation is through communicating veins, any one of which may become an abnormal channel through which the "head" of pressure may be exerted

Many physiological tests have been devised to determine patency of the valves and the relationship of the superficial to the deep circulation

Von Perthes Test A tourniquet is applied to the thigh tightly enough to obstruct the long saphenous vein The leg is then exercised by repeated flexion or walking and the prominence of the veins is noted If the deep circulation and the communicating veins are competent, the blood will disappear from the superficial veins which will collapse If

elicited in any part of the skin in which the sensory nerves have degenerated

H Substance. Lewis explained the phenomenon by stating that the cells of normal tissues contain what he called "H Substance" The "H Substance" is liberated from the cytoplasm in a diffusible form whenever cells are injured It causes the adjacent capillaries and venules to dilate and renders them unresponsive to substances or nerve stimuli which normally would induce the capillaries or venules to constrict

If the local sensory fibers are intact, an axon reflex causes dilatation of the regional arterioles and increases the blood flow through the part These dilated arterioles produce the flare

Histamine is a substance which is found in traces in normal tissue Its precursor, histidine, is an amino acid present in all living tissue in considerable amounts Histamine experimentally causes dilatation of the capillaries by direct action on the capillary walls It has been suggested that amounts sufficient to produce this paralyzing effect upon the capillaries may be liberated from damaged tissues

THE VENOUS SYSTEM

The venous circulation depends chiefly upon the following mechanical factors 1. Contraction of the skeletal muscles propels the blood towards the heart, valves in the veins preventing its flow in the reverse direction There is also some evidence that the vein wall itself is contractile 2 Negative pressures produced by respiration combined with the increase of intra-abdominal pressure during the descent of the diaphragm are important in maintaining venous blood flow 3 A slightly positive pressure in the veins and capillaries (6 to 10 millimeters of mercury) tends to increase venous flow If there is arteriolar dilatation with atony, the venous pressure and flow increase 4 Gravitation assists venous return above the level of the heart and retards it below 5 Increase in blood volume promotes venous flow and the reverse is true when blood volume is decreased 6 Loss of capillary tone in shock results in pooling of blood with decrease in venous pressure and blood flow 7. Vasomotor control, similar to that of the arterioles, influences venous blood flow Sympathetic stimulation causes a reaction in the vein wall

Nervous Intervention The veins are innervated and regulated by a mechanism similar to that of the arterioles The sympathetics exert a tonic constrictor influence and sympathectomy produces dilatation of the veins Pressor reflexes cause contractions of the vessels Increased carbon dioxide tension in the medulla causes venous constriction

short time and then actually develops into typical thrombophlebitis They indicate that all degrees of inflammation may exist

Thrombophlebitis Acute thrombophlebitis is an inflammatory thrombotic process which is most commonly found in the veins of the lower extremity It first manifests itself in the larger radicals of the femoral venous system and usually progresses peripherally against the circulation Pain, edema of the extremity, fever and leukocytosis are characteristic clinical manifestations The important factors involved in its production are slowing of the circulation from mechanical interference, trauma, operative or nonoperative infection and muscular inactivity as associated with long periods of bed rest The common occurrence of thrombophlebitis as a complication of pregnancy is well recognized and probably is an indication of the effects of both stasis and trauma

Suppurative or bacterial thrombophlebitis is rare Chronic inflammation of the vessels may follow injections of various chemicals, but the overwhelming majority of cases are included in a category of spontaneous or idiopathic thrombophlebitis

Alterations in function in the inflamed venous system result from obstruction of blood flow with an increase in local venous and capillary pressure The extent of the change will be in inverse proportion to the extent of available collateral circulation Associated with obstruction is severe spasm of both the arterioles and venules further embarrassing venous circulation The resulting capillary stasis produces increased capillary permeability with resultant edema The lymphatic vessels which normally play an important role in removing tissue fluid may become inadequate This results from acute venous obstruction with lymphatic overloading and from tissue hypoxia produced by arterial insufficiency

Phlebothrombosis Phlebothrombosis is characterized by the formation of a bland thrombus in the lumen of the vein The initial inflammatory reaction is either absent or minimal and local clinical response is often minimal General reactions such as fever, leukocytosis and pain are absent or slight Minimal tenderness may be detected in the calf on physical examination

The disease process usually begins in the smaller channels of the femoral tree and progresses in the direction of the blood stream as the thrombus grows in length. The soft clot can break off into the blood stream and produce serious or fatal emboli

Venous congestion and edema are not prominent. The basic phy-

the saphenous veins remain unchanged there is an incompetence of the communicating veins Engorgement of the saphenous veins associated with pain indicates incompetence of the communicating branches, and of the deep circulation

Ochsner and Mahorner "Comparative Tourniquet Test": The technic in Von Perthes test is employed at the upper, middle and lower thigh Thus, the exact location of the incompetent communicating veins may be ascertained For example, if the veins below the lowest test point collapse, but the veins below the midthigh tourniquet do not, the incompetent communicating veins may be found in the zone between the tourniquets

Brodie-Trendelenburg Test· The so-called Trendelenburg test was first described by Brodie in 1846 The maneuvers are 1 Drain the veins of their blood by elevation of the extremity with the patient in the recumbent position 2 Apply pressure over the upper saphenous vein to keep it obstructed and have the patient stand 3 Release the pressure rapidly 4 Repeat these maneuvers, maintaining pressure over the upper saphenous for thirty-five seconds after the patient stands

The result is "positive" if the varices fill rapidly from above when pressure is released, but fill slowly and incompletely when pressure is maintained This indicates incompetency of the valves of the greater saphenous vein but competency of the valves of the communicating veins The result is "double positive" if the varices fill rapidly after rapid removal of pressure and during maintained pressure This indicates a patency of the long saphenous valves and the communicating vein valves The result is negative when there is only very slow incomplete filling with both rapidly released and maintained pressure This suggests competency of both the saphenous and communicating valves

De Takats and his associates found a uniform increase in the content of carbon dioxide and a decrease in oxygen in blood from the lower limb containing varicosities as compared with the upper extremity

Venous Thrombosis The terms thrombophlebitis and phlebothrombosis have been employed to describe two types of venous clotting Homans was the first to distinguish the type of "bland" thrombosis from the more commonly recognized inflammatory type Ochsner and De Bakey further clarified the two types of thrombosis and suggested the term "phlebothrombosis" for the bland, noninflammatory thrombosis responsible for pulmonary emboli, as compared with term "thrombophlebitis" for the inflammatory adherent type Allen and his associates, however, are of the opinion that the bland thrombus exists for only a

short time and then actually develops into typical thrombophlebitis They indicate that all degrees of inflammation may exist

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Venous congestion and edema are not prominent The basic physio-

logical changes are to be found in the changed blood coagulation system There is an increased viscosity and an increase in thrombocytes, fibrinogen and leukocytes Clinical application of the variation in blood viscosity has been studied by Shadid His test indicates that changes in blood viscosity often precede thrombus formation Certainly, in phlebothrombosis there is a generalized change in blood coagulability which tends to manifest itself in areas of decreased flow Upon these principles is based the concept of anticoagulant therapy

The work of Kaye indicates the importance of the roles of vitamin E and adrenal cortical hormone in the problem of hypercoagulability It is possible that some protection is furnished by the administration of a tocopherol acetate and adrenal cortical hormone

Chronic Thrombophlebitis, Chronic Venous Insufficiency. The late manifestations of chronic edema and venous obstruction are evident in chronic thrombophlebitis Accumulated interstitial fluid produces secondary fibrosis of the subcutaneous tissue characterized by edema, skin pigmentation and pretibial ulceration

The varicose ulcer is the end point of the processes of vein dilatation, weakened valves and venous stasis The increase in capillary stasis and pressure will interfere with nutritional and oxygen exchange in the tissues Anoxia reduces the resistance of the tissue to trauma and the slightest contusion or abrasion may be followed by chronic ulceration This condition is aggravated by concomitant lymphatic obstruction Trout has indicated that the typical pigmentation of the skin prior to ulceration is due to failure of the venous and lymphatic channels to remove certain of the blood pigments

✓ Blood Pressure: Four principal factors maintain blood pressure Cardiac output, blood volume, blood viscosity and peripheral resistance Assuming the first three factors are constant, increased tonus even in a small portion of the vascular bed may produce a significant rise in systemic blood pressure Despite the hypertension, however, the volume of blood flow remains the same since the increased pressure neutralizes the resistance This mechanism accounts for the findings of Prinzmetal and Wilson, who were able to demonstrate that the blood flow in a patient with hypertension and the normal subject is approximately the same If, however, a large reservoir is involved, such as the splanchnic vessels, Abramson and Fierst have shown increase in blood flow in the upper extremity in patients with hypertension

Hypertension The systems involved in hypertension, according to Page, are shown in Table I

✓ Hypertension Produced by Experimental Methods Selye and

TABLE I

SYSTEMS INVOLVED IN HYPERTENSION

Clinical	*Experimental*
I Nervous Participation	
Poliomyelitis of brain stem	Cerebral ischemia.
Porphyria.	Cushing's experiment
Increased intracranial pressure	Resection of sinus and aortic depressor nerves
Sclerosis of carotid sinus.	Hypertension from audiogenic stimulus.
Resection of glossopharyngeal nerve	
Emotion.	
II Cardiovascular Participation	
Coarctation of aorta	Clamping of aorta above renal vessels.
Heart Failure.	
Arteriovenous fistula.	
Arteriosclerosis.	
III Endocrine Participation	
Hypophysis—basophil adenoma	Anterior lobectomy diminishing blood pressure
Adrenals—Pheochromocytoma	Adrenalin hypertension.
Cortical carcinoma	Desoxycorticosterone acetate hypertension
Cortical hyperplasias.	Bilateral adrenalectomy abolishes hypertension
Thymus—Carcinoma with Cushing's syndrome	
Placenta—associated with toxemia of pregnancy	
IV Renal Participation	
Glomerulonephritis	Antikidney serum nephritis
Obstruction of renal vessels.	Mechanical constriction of renal arteries or veins
Pyelonephritis.	Mechanical compression of ureters.
Prostatic obstruction	Cellophane or silk perinephritis.
Polycystic kidneys.	
Crush syndrome	
Periarteritis nodosa.	
Perinephric constriction of the parenchyma.	

his associates have demonstrated that desoxycorticosterone acetate when given after unilateral nephrectomy in female rats, mice or chicks receiving salt in their drinking water causes severe nephrosclerosis moderate hypertension and associated vascular changes An emulsion of anterior pituitary gland also produces much the same result possibly because of influence on the adrenal cortex

The production of hypertension by steroids has its striking clinical counterpart in the hypertension of Cushing's syndrome

Experimental renal hypertension simulates more closely essential

hypertension in human beings than other forms of the disease The nervous participation in renal hypertension seems to be unimportant Severance of the renal nerves neither lowers blood pressure nor prevents elicitation of hypertension. Page indicates that even "total" sympathectomy does not decisively influence renal hypertension In this regard reference is made to vasopressor substances found in the spinal fluid in animals suffering from renal hypertension

The endocrine participation in hypertension of the experimental renal type is according to most recent work, associated with adrenalin gland physiology particularly that of the cortex Though removal of the pituitary in animals produces a drop in blood pressure this is apparently through the agency of the adrenal cortex since pure adrenocorticotropic hormone can counteract this effect Bilateral adrenalectomy produces a decrease of renal hypertension to normal levels, but salt administration alone does not counteract this The complete removal of the adrenals produces a decrease in renin substrate the protein upon which renin acts to produce the pressor angiotonin With the administration of hormone this substrate returns to normal concentration

The response of the blood vessel wall itself is important There is evidence that there is augmented sensitivity of the arteriolar wall in the hypertensive patient and in the experimental animal In this respect the report of Carlos Jimenez Diaz is interesting He believes that the hypertensive factor arises from the production of a hormone in the arterial wall by the action of sympathetics or some substance in the plasma

The Surgical Treatment of Hypertension. The application of surgical therapy to hypertension has been based on the concept that the basic and most prevalent pathogenetic mechanism is overactivity of the sympathetic nervous system Furthermore it is conceived that the stimulus for this hyperactivity comes from the central nervous system *and is an expression of emotional effect The individual variation and* the hereditary factor indicate a difference in the sensitivity of the vascular substrate Craig has reviewed the various types of operation for hypertension indicating the physiological consequences to be expected The excision of portions of the sympathetic chain and its ganglion appears to be the most effective operation as indicated by the work of Smithwick who first combined supra- and infra-diaphragmatic sympathectomy *Grimson Craig Peet* Hinton *Poppen DeTakats and others* have made fundamental contributions to the subject

The effects of sympathectomy depend largely upon the lability of the vascular tree Dependable physiological evidence of lability is

difficult to obtain Attempts have been made, however, to test this preoperatively by using the effects of rest and response to barbiturates, ganglion depressants such as the tetraethylammonium drugs and cold pressor tests All of these are designed to block the sympathetic pathway at some point, i e, emotional, central, ganglion and myoneural sympathetic juncture in the vessel wall None of these physiological gauges forecasts dependably the results to be obtained The clinical observation of the patient and his responses probably form the best general index

Postoperative side effects after sympathectomy are noteworthy 1 Syncope with orthostatic effect which is believed to be due to central anoxia caused by sudden pooling of blood in the lower vascular tree 2 Hyperhidrosis in the area not affected by the operation as a compensation in the heat regulating mechanism 3 Anhidrosis in the affected area with moderate tendency for dryness of skin 4 Marked decrease or absence of headache irrespective of the effect on the blood pressure

A summary of the physiological background of hypertension indicates 1 It is a condition in which the vascular resistance is increased by arteriolar spasm 2 This spasm is produced by a vasopressor blood element, i e, angiotonin, or the effect of adrenal cortex pituitary sodium ion metabolism 3 The neurogenic effect of an overactive vasomotor system 4 The properties of the arteriolar wall itself

Surgical treatment is designed to increase the vascular bed and thereby decrease resistance and blood pressure

Postural Hypotension In cases of postural hypotension, it appears that the vasomotor control of the arterioles is diminished or absent Numerous investigators have patients with the disease who do not respond with the normal reaction of vasoconstriction to the stimuli of pain position and so forth Head and Ebert felt that the normal reflex vasoconstriction, in response to a fall in arterial blood pressure, is absent in postural hypotension Since peripheral galvanic stimulation of the blood vessels produces angiospasm it is concluded that the defect exists in the vasomotor center MacLean and Allen have presented the view that there is no deficiency in arteriolar tone but rather a slowing of the venous return to the heart

Role of the Peripheral Circulation in Heat Regulation The skin plays the principal role in the balance between heat production and heat loss At least 70 per cent of the total elimination of heat from the body takes place through radiation conduction and convection from the skin The transfer of heat from the internal parts to the skin is carried out by the circulatory system The cutaneous blood flow through

the four extremities composes 65 per cent of the total body surface

The application of heat to a small area produces local dilatation of arterioles, capillaries and veins As a result of increased blood flow, capillary filtration pressure increases and temporary edema is produced Toleration of heat decreases with decreased blood flow so that if the blood supply of an extremity is diminished and subjected to heat, burning pain is increased and a greater heat penetration can be demonstrated This fact is of fundamental importance in the contraindication for applying direct heat to ischemic tissue

Effects of Heat and Cold: The increased metabolic rate produced by heat effects an increase in blood flow by increasing oxygen need, thereby the anoxic imbalance persists Since the vasodilatation also occurs at a distance, the physiological effects and therapeutic response to indirect heat is to be understood Gibbon and Landis produced dilatation of the lower extremity vessels by immersing the forearms in warm water This effect was not produced when the blood from the heated limb was prevented from reaching the heart Their conclusion was that the heated blood produced its effect on the temperature regulatory center

Application of cold produces vasoconstriction by direct action of the stimulus on the blood vessels Vasodilatation may follow so that, according to Lewis, there are alternating cycles It is his concept that the vasodilator mechanism involves the release of a histamine-like substance due to mild tissue injury This refers to the local application of cold If, however, external cold is applied to the whole body, peripheral vasoconstriction and an elevation of metabolism occur as a result of muscular tone and shivering Brown, Wise and Wheeler found that moderate cooling of the forearm increased the extravascular volume of the forearm, decreased the rate of filtration produced by a given rise of venous pressure, and decreased the rate of reabsorption of extravascular fluid These effects were attributed to increased capillary permeability particularly with respect to protein Cold, by producing arteriolar constriction and increased capillary permeability, sets into operation two opposing forces, hydrostatic and osmotic, in such a way that adequate tissue fluid formation may take place with a small blood flow Decreased reabsorption resulting from protein leakage and reduced capillary surface will result in tissue edema if cold and the increased venous pressure of dependency are combined

If the body is subjected to long periods of heat or cold the response differs from the reaction to acute intense heat or cold With moderate prolonged cold heat regulation is accomplished by vasoconstriction of

the cutaneous circulation, a decrease in blood volume and a greater heat production through endocrine effects The opposite occurs with prolonged moderate heat

Considerable evidence has been presented to indicate that all portions of the extremities are not equally important in the function of heat dissipation and conservation. It has been generally accepted that the circulation through the hands has only in part the function of satisfying the oxygen requirements of the skin and bone The major portion of the blood flow has to do with the matter of heat dissipation The theory that the arteriovenous anastomoses are involved in this function has been indicated These vessels, which are richly supplied with sympathetic fibers, can readily dilate or constrict thus shunting the blood from arterial to venous side without traversing the capillary bed In this manner large amounts of heat can be disseminated It can be concluded, therefore that the high resting blood flow through the hand under ordinary environmental conditions serves primarily the function of heat regulation rather than oxygen transport, while the much lower circulation in the forearm and leg probably is related to the local metabolism

Role of the Circulation in Response to Effort The general adjustment of the cardiovascular system to exercise is in response to increased metabolism and at the same time makes provision for the maintenance of an adequate supply of blood to such vital organs as the brain, heart and lungs Increased cardiac output is one of the fundamental adjustments to exercise. The increase in minute volume output is dependent upon an increased venous return which is accomplished by increased pumping action of the skeletal muscles Since the venous system is freely supplied with valves which prevent regurgitation of blood, the muscle force propels the venous blood only toward the heart Another mechanism which increases cardiac minute volume output is acceleration of the pulse rate

To maintain adequate circulation of the tissues, an increase in blood pressure occurs with exercise The diastolic pressure is not affected to the same degree as the systolic, thus increasing the pulse pressure In addition there is a compensatory vasoconstriction in a nonaffected region, such as the splanchnic area

Another general change in response to effort studied by Kaltreider and Meneely, and Dill is the concentration of serum proteins, blood cells and hemoglobin This is produced by the passage of protein poor fluid from the vascular system into the interstitial spaces

The local physiological effects of effort are noteworthy According to

several investigators, an increase in blood flow through the muscles occurs during exercise, with definite increase in heat production This heat is transferred to the skin to some extent Gaskell indicated that the increase in blood flow is due to the liberation of vasodilator substances from the active muscle fibers This chemical response was evidently independent of the vasomotor system since it occurred after sympathectomy and somatic nerve degeneration

A number of vasodilator substances such as histamine, acetylcholine and adenylic compound have been implicated in the hyperemia from exercise

Associated with local effects are reactions in distant parts of the body Ellis found a higher venous oxygen concentration in blood taken from the arm during the period of leg muscle exercise He interpreted this finding as indicating a greater blood flow through the upper extremities as well as the lower

In addition to more rapid circulation of blood, the increase in oxygen consumption is also met by a greater utilization of the oxygen in the blood The venous blood under resting conditions ordinarily has approximately 75 per cent oxygen saturation, whereas, with exercise this may drop to 20 to 30 per cent for blood leaving active muscles Two mechanisms lead to this—a greater dissociation of oxyhemoglobin and a decrease in affinity of venous blood for oxygen

Intermittent Claudication Intermittent claudication is local pain occurring during exercise in muscles with inadequate blood supply Lewis believed that the pain is due neither to oxygen lack nor to vascular spasm, but rather to the accumulation of a substance within the muscle which he called factor "P" Though this factor accumulates during ischemia, it is removed quickly with restoration of blood supply and increased oxygenation

Local Anoxia A decrease in relative oxygen supply to tissues may be the result of changes in the vessels or the state of the tissue itself The increase in oxygen requirement by the tissues, superimposed upon a relatively poorly adjusted blood supply, increases the degree of hypoxia This becomes of clinical importance in relation to the problem of applying heat to ischemic extremities Sufficient heat applied for long enough periods of time will elevate the metabolic needs and further unbalance the ratio of supply to demand The resultant anoxia may reach sufficient proportions to produce tissue necrosis in the form of ulceration or gangrene The additional danger of thermal burns due to inability to adjust to heat regulation mechanisms must be kept in

mind. Similarly, the cooling of the anoxic extremity decreases the local metabolic rate and thereby decreases oxygen need

The blood itself influences the state of anoxia depending upon its ability to carry sufficient oxygen The concentration and level of hemoglobin is pertinent to this Anemia affects adversely the delivery of oxygen to the tissues The degree of oxygenation of hemoglobin is in turn influenced by the efficiency of cardiac and pulmonary function Primarily, however, the principal factor in tissue anoxia is decreased blood supply due to vascular cross sectional bed changes, i e , ischemia These changes stem from functional or spastic phenomena and organic changes in the vessel wall The balance between blood supply and tissue need may be compared to a scale in which either increased tissue need or decreased oxygen supply may tip the balance toward anoxia

Limb Volume and Local Blood Flow Under normal physiological conditions the hand and foot are intermittently changing in volume, largely as a result of alterations in the quantity of blood present in the veins, muscles and capillaries The capacity of the vascular bed is dependent in great part upon the changes in venous tone The integrity of the arterial inflow is important in altering volume, but functions in conjunction with nervous and venous mechanisms

Hemometakinesia It is important to consider the "borrowing lending" mechanism aptly described by De Bakey, Ochsner and associates under the term "Hemometakinesia." They point out that there is a continuous shifting of blood from one part of the body to another. This borrowing and lending to meet variations in local requirements seem to indicate a well regulated mechanism which permits the body to utilize its limited total blood volume in the most efficient manner The essence of this mechanism seems to lie in the control and regulation of the vascular bed, which permits an increase in the volume of blood in one part of the body with corresponding decrease in other parts Total blood volume changes occur as a gradual response, but the shifting of blood mass may be a rapid adjustment

These principles of hemodynamics are applicable to the management of peripheral vascular disease General measures to affect the whole vascular mechanism do not increase, selectively, blood flow to a given portion of the vascular tree Local effects from sympathetic block or sympathectomy, however, are selective

Hormonal Influence on Peripheral Circulation Moderate doses of epinephrin produce increased muscle blood flow, both in experimental animals and man This occurs even in extremities which had been de

prived of sympathetic innervation Skin vessels, arterioles, capillaries, venules and veins, however, are constricted at the same time that muscle vessels are dilated

The response of the vessels to epinephrin after sympathectomy is noteworthy Numerous authors have presented evidence in favor of the concept that sympathectomy renders vessels more sensitive to circulating epinephrin According to White, sensitiveness to adrenalin is manifested regardless of whether postganglionic or preganglionic neurons are destroyed He believes that denervated smooth muscle in the arterial walls becomes sensitive as the vasomotor nerves degenerate Apparently the response is much greater after destruction of the postganglionic neurons than after section of the preganglionic fibers

Pitressin has little effect on the general circulation It may produce vasoconstriction in the skin vessels and in addition is responsible for pooling of blood in the veins by mechanisms which are not understood

The peripheral vascular changes associated with the injection of massive doses of insulin have been studied by Abramson and his associates They found a significant increase in blood flow when measured by the venous occlusion plethysmograph This flow was greater in the forearm and hand than in the leg These reactions may be related to circulating epinephrin or adrenal-like substances which appear to be produced during the hypoglycemic state

The sex hormones, theelin in the female and testosterone in the male, may produce an increase in blood flow, but available evidence is contradictory Stilbestrol, the synthetic estrogenic substance has been shown to increase circulation to the hand

Raynaud's Disease Alterations in blood flow in Raynaud's disease occur in the digital arterioles Changes which occur in the capillaries and venules are probably secondary to stasis resulting from slowing of the blood flow in the arterioles The pallor of the effected part results from spasm of the arterioles and during this stage the capillary microscope will reveal that blood is not entering the capillaries During the stage of cyanosis, the blood in the capillaries is stagnant and an unusual number of capillaries are dilated

Raynaud referred to the condition as a derangement of the nervous system, but Adson and Brown believe that in early Raynaud's disease the abnormality is wholly in the vasomotor system, however, other investigators do not agree Lewis and his associates concluded, after an intensive study, that the primary factor lies in a fault in the digital arteries in the form of an abnormal sensitivity to temperature At present the evidence indicates both local and general vasomotor faults

That psychosomatic factors are of importance is well recognized

Scleroderma It has been suggested that in addition to the arteriospastic aspects of the Raynaud's phenomenon associated with scleroderma, there is an increase in connective tissue around the blood vessels which may constrict them and lead to ischemia Prinzmetal concluded that the factors affecting the peripheral circulation in scleroderma are the tight inelastic skin and subcutaneous tissues which constrict the circulation

Erythromelalgia Of the various disturbances which make up the syndrome, erythromelalgia, the increased skin temperature is the most important and most constant Ranges from 89 to 97 degrees F are common

Vasodilatation accounts for the wide swing in temperature Burning pain accompanies the inordinate vasodilatation There is an increase in arterial pulsation which produces throbbing and increase in venous blood oxygen content

The burning distress may be precipitated by applying a pneumatic cuff over the area involved If the extremity is held dependent, this also occurs, and is relieved by elevation, though the skin temperature remains unchanged

Acrocyanosis This disease is characterized by cyanosis and coldness of the hands and feet generally associated with marked hyperhidrosis, Various explanations of the physiological changes include 1 There is an obstruction to venous return due to increased tone of the subcutaneous veins 2 There exists capillary and venule dilatation due to vasomotor or organic changes 3 There is an increase in tone in the arterioles of the skin which diminishes the flow into the capillaries and produces stasis of poorly oxygenated blood in the subpapillary venous plexuses

Since sympathectomy has produced alleviation, the concept that there is a vasomotor derangement seems well founded

Posttraumatic Vasomotor Disorders Shumaker and Abramson have given the name posttraumatic vasomotor disorders to a group of dystrophies first described by Sudek in 1900 In these cases an injury to an extremity produces, in addition to direct trauma effect, what appears to be some reflex disorder initiated by irritation from the local tissue damage The syndrome is that of reflex sympathetic overactivity, which with the periarterial edema accompanying it, produces atrophy, pain swelling, coldness cyanosis and edema Excessive sweating also results Sympathectomy produces beneficial results

Causalgia Available evidence indicates that part of the mechanism

of causalgia involves a disturbance in the control of the blood vessels In particular, overfilling of the minute vessels at the periphery can readily account for the signs and symptoms, e g , burning pain, hot, red skin and occasional herpetic eruptions Moreover, the measures which are partially successful in treatment are those which prevent overfilling of the small vessels Elevation of the part relieves the pain Temporary relief by compression of the radial and posterior tibial artery has been reported and occasionally ligation of these vessels has completely abolished the pain

Immersion Foot "Immersion foot" is a term applied to a condition which develops from prolonged immersion of the feet in cool or cold water It is also very closely related to the conditions given the name Pernio and Chilblains Apparently the common denominator of all these states is vasospasm in the arterioles affected by cold The degree and duration of the injury, together with the individual sensitivity to cold, produce the disorder In immersion foot there is an initial vasospastic, a hyperemic and a late vasospastic stage To the vasospasm of the initial stage is added the troublesome cyanosis and edema which probably are due to resultant stasis from prolonged dependent position exposure

Frost Bite· Frost bite is the most frequent disorder produced by exposure to cold The effect of cold is augmented by dampness, contact with metal, high wind, and any already existing ischemia in the extremity At the first the effect is almost entirely arteriolospastic, but as the cold increases in severity and duration arterial thrombosis with further ischemia follows Tissue death may occur from direct freezing of the cellular fluids with crystallization and formation of ice

Johnson finds that the intravascular clotting characteristic of frost bite does not occur until four or five hours after the trauma Because of this, he advocates the use of heparin to prevent clotting Cold, by producing arteriolar constriction and increased capillary permeability, sets into operation two opposing forces, hydrostatic and osmotic, in such a way that adequate tissue fluid formation may take place with a small blood flow At temperatures which produce cold injuries, the rate of oxygen dissociation is also decreased resulting in greater hypoxia

Sudden Occlusion of the Arteries *Embolism, Thrombosis* The ligation of an artery in continuity may cause diminished blood flow at the periphery leading to impoverishment of nutrition of the tissues That this result is not due solely to the mechanical obstruction of the

circulation at the point of ligation, but chiefly to reflex vasomotor changes in the peripheral vessels themselves, is indicated by the fact that ligation of the artery in two places and division between the ligatures may be followed by vasodilatation, warmth and other evidences of an adequate flow of blood in the tissues peripheral to the point of division In fact, cases have been recorded in which considerable lengths of the main artery supplying an extremity have been excised completely, yet the extremity on the affected side has remained warmer than that on the opposite side The difference between the effects of ligation and the effects of excision of an artery can be explained by assuming that in the case of excision vasoconstrictor nerve impulses are prevented from reaching the peripheral vessels Leriche considers an obliterated artery as a diseased plexus of sympathetic nerve fibers provoking distal vasospasm in the network of the anastomotic vessels Collateral circulation is established more quickly and more effectively after arterial resection than after ligation

Harvey demonstrated that following high arterial ligation in the extremities of dogs, collateral circulation did not develop gradually, but instead returned abruptly after an interval of six to 12 hours He believes, therefore, that this sudden development of collateral circulation is not a purely mechanical affair, but that the mechanism responsible for it must be a vasomotor one largely Sympathectomy (lumbar ganglionectomy) as a preliminary to obliteration of an aneurysm of the popliteal artery has been performed by Bird, to reduce the danger of postoperative gangrene from vasospasm. For all aneurysms of the large arteries of the lower extremity, Gage recommends preoperative injection of the first, second and third lumbar sympathetic ganglia on the same side as the aneurysm with 95 per cent alcohol. He also recommends that aneurysms of the upper extremity be treated by surgical removal or repeated injections of the stellate ganglion with one per cent procaine hydrochloride Alcohol injections are contraindicated because of the high incidence of alcoholic neuritis of the brachial plexus He reports successful employment of these measures in over 15 cases of both arterial and arteriovenous aneurysms of the peripheral arteries

In different types of sudden obstruction of the large arteries the incidence of gangrene varies greatly In embolic *obstructions and fol*lowing ligations of traumatic lesions, the incidence of gangrene is high, whereas in ligations for aneurysm and ligations for arteriovenous aneurysms, the incidence is low In the latter cases there is prolonged

interference with the flow of blood through the normal channel prior to operation, so that the collateral vessels become accustomed to carrying an increasing proportion of the blood

In cases of all types just mentioned, Gage and Ochsner recommend preoperative "chemical section" of the cervicodorsal and of the lumbar sympathetics, for the arms and legs respectively, to prevent ischemic gangrene They emphasize that the collateral arteries and arterioles are under the control of the same system of sympathetic vasomotor nerves which controls the main arteries They caution that ether anesthesia releases vasospasm and increases peripheral blood flow as much as does sympathectomy If ether is used, therefore, the collateral circulation may appear adequate at the time of operation, but ischemia may set in some hours later

The so-called "development of a collateral circulation" really means in most, if not in all cases, the "activation of the collateral circulation," that is, the dilatation of collateral blood vessels normally present

Thrombophlebitis can cause harmful reflex vascular disturbances which have proved amenable to treatment by interruption of sympathetic pathways In thrombophlebitis, McKechnie and Allen observed that arterial pulsations may be absent temporarily, apparently because of spasm In sudden arterial occlusion, they believe that ischemia is not an adequate explanation for the severe pain, and that the ischemia is too profound and extensive to be caused by the localized organic occlusion alone They agree with those who attribute both the pain and the ischemia chiefly to arterial spasm, and favor regional, spinal or general anesthesia as a means of removing the spasm, rather than sympathectomy as previously suggested by Theis Seifert and others have observed directly spasm of the involved artery during operation for embolectomy

Arteriosclerosis Obliterans Arteriosclerosis obliterans may be defined as that type of arteriosclerosis, occurring typically in the extremities, which eventually results in progressive episodal occlusion of arterial lumina

The etiology of this condition has been the subject of intensive study for many years since the first comprehensive description of the atheromatous lesion by Virchow in the middle of the nineteenth century According to Allen Barker and Hines, of the theories which have been proposed, two principal ones are tenable at the present time—the mechanical and the metabolic

The mechanical concept first propounded by Virchow suggests that the arterial wall changes are due to the wear and tear of repeated

trauma of pulsations and intra arterial bombardment. With aging, the elastic and smooth muscle tissue tends to lose its elasticity and weakens The disease process is so much more common in the lower extremities because the pressures are greater in this part of the arterial bed.

The propensity of the sclerotic process to develop in certain parts of the body in certain families leads to the conclusion that there exists a hereditary vascular tendency Virchow and Aschoff believed that there was loosening of the ground substance in the subintimal region and that subsequent changes of elastic and fibroblastic tissue with degeneration heralded the approach of the atheroma which thus represents fat replacement A study of amputated legs from patients with arteriosclerosis, by Schlossman and Gerber, in which several sections of the vessel wall, at all levels, were made, demonstrated lesions of the subintimal region preceding atheromatous degeneration Amorphous change in the fibroblasts could be detected as an evidence of early change Such phenomena had been described previously in the coronary arteries by Horn and Finkelstein

Disturbance of cholesterol and lipid metabolism is a favored theory to explain atheromatous changes in blood vessels Aschoff first pointed out that the higher the plasma cholesterol content, the greater the subintimal deposition

A summary of the evidence to date indicates that arteriosclerosis may begin primarily as a mechanical injury associated with age or wear and tear and that disturbances of lipoid metabolism, particularly when associated with lipemia, tend to accelerate the development of the atheroma. This is particularly true in the presence of diabetes mellitus

The altered vascular physiology in arteriosclerosis has always been recognized to be due partially to mechanical interference However, not until recent years has the factor of superimposed arteriospasm been taken seriously Studies of patients with the disease show a lack of exact correlation between degree of tissue hypoxia and degree of organic change There is an additional variable of spasm in each individual

As pointed out by Leriche, it is probably true that any organic disease of the vessels may in addition to mechanical interference with the local circulation produce vasomotor disturbances reflexly, especially vasoconstriction in the lesion itself and in the region distal to it Clinical experience indicates positive response of this vasoconstriction to procaine injections or excision of the sympathetic ganglion and chain Numerous workers including Flothow DeTakats, Coller, Ger

ber, McCune, Eastman and Blain, have shown an extremity salvage rate following sympathectomy which is 24 per cent higher than in patients on general care only

The response of arteriosclerosis to sympathectomy is unpredictable, and there is very poor correlation between reaction to procaine sympathetic blocks and to sympathectomy Uncommonly, the sympathetic denervation may aggravate the tissue hypoxia and precipitate or accelerate necrosis This may be the result of postdenervation thrombosis or of paralysis of the arteriovenous shunt in dilatation so that more blood short circuits the capillaries and, therefore, the tissues, or the result of pooling of blood in the arteriolar-capillary venule loop

In addition to mechanical obstruction and vasospasm, thrombosis plays a vital role in alteration of local physiology As shown by Horn and Finkelstein, on coronary vessels, and Schlossman and Gerber, on vessels of the legs, the most common precursor to the thrombus is rupture of the arteriosclerotic plaque The entrance of tissue into the lumen quickly produces thrombosis However, thrombosis may and does occur on the basis of stasis, or adherence of blood elements without rupture of a plaque The degree of incompetency is dependent on the size of the thrombosis, its position and the rapidity of occurrence Clotting increases the arteriospasm The need for maintaining blood fluidity, anticoagulation and prevention of trauma to the area is established by these findings

The diabetic patient's response to arteriosclerosis is similar to that of the nondiabetic The disease occurs earlier in life, however, and the complication of infection is more common

Thrombo-Angiitis Obliterans *Buerger's Disease* Thrombo-angiitis obliterans is a segmental, inflammatory, obliterative disease of the arteries and veins which occurs almost exclusively in young men It involves the extremities and rarely the viscera Ischemia of tissues is produced which can be followed by gangrene The disease, though described in numerous isolated unrelated reports previously, was first analyzed and a large number of cases presented by Buerger in 1908 His book published in 1924 is a most complete study

Study of altered physiology in thrombo-angiitis obliterans has extended not only to the altered circulation but to the blood as well Koga and others have reported that increased blood viscosity was present in the disease This was explained on the basis of reduced blood volume by Silbert and Friedlander, who showed that administration of thyroid increased the blood volume to normal level

Rabinowitz and Kahn found an increase in phospholipids in the

blood in cases of thrombo-angiitis obliterans and large amounts of choline excretion in the urine They also reported an increase in the cephalin lecithin ratio in plasma which, they felt, predisposed to intra vascular clotting

Theis and Freeland demonstrated increased viscosity of the blood, rapid sedimentation of the cells, rapid coagulation of blood, greatly increased alkalinity and low oxygen saturation of arterial blood These findings were present in the "acute" process or in exacerbations of the chronic one

Studies by Roth, Maclav and Allen indicate no abnormal blood levels for any blood components This is particularly noteworthy in the normal values, except in a few cases, of the phospholipids They did find an increased oxygen tension in the venous blood of cases with advanced ischemia There is, therefore, no clear indication that the state of the blood plays an important role in the altered physiology of thrombo-angiitis obliterans Increase in blood viscosity seems to be well corroborated

The change in blood circulation in thrombo angiitis obliterans occurs as a result of the interaction of three pathological phenomena—arterial occlusion, arterial spasm and thrombophlebitis The degree of arteriolar spasm varies in individuals but may be so severe as to produce a typical Raynaud's phenomenon The spasm far exceeds the spasm found in arteriosclerosis The deleterious effects of the use of tobacco in patients with thrombo-angiitis obliterans is well known

Sympathetic nerve interruption or sympathectomy is relatively effective in the therapy of thrombo-angiitis obliterans Periarterial stripping has not been as satisfactory as ganglionectomy The opera tion does not affect the pathological process but does provide maximum arteriolar dilatation and maximum collateral response It prevents gangrene in progressive cases though it is ineffective if a large vessel is involved through a long segment

Arteriovenous Fistulas (Aneurysm) An arteriovenous fistula is an abnormal communication between an artery and a vein The condi tion was first described by William Hunter in 1757 Holman has authoritatively outlined the immediate physiological changes in ex perimental arteriovenous fistula 1 A fall in arterial blood pressure diastolic as well as systolic 2 An increase in pulse rate 3 Increase in venous pressure, proximal as well as distal to the fistula 4 Increase in cardiac output, depending on the size and location of the fistula 5 Temporary decrease in the size of the heart and of the artery proximal to the fistula due to the sudden diversion of blood to the

capacious venous system, an alteration comparable to that seen in massive hemorrhage

The more remote effects from arteriovenous fistula are 1 A permanent diversion of part of the circulating blood from the normal capillary bed into the fistulous circuit 2 A gradually increasing blood volume in proportion to the amount of diversion at the fistula 3 A gradual dilatation and slight hypertrophy of the heart, and of the artery and vein proximal to the fistula, from the distending effect of an increased volume of blood attracted to the fistulous circuit because of its lessened resistance 4 The development of an extensive collateral circulation 5 The blood pressure returns to normal at the systolic level but not at the diastolic, thereby producing an increase in pulse pressure

The volume of blood diverted depends upon the size of the fistula, its location in the arterial tree, and the absence of any obstruction in the vein proximal to it

Elkin and Warren's observations of physiologic changes with arteriovenous aneurysm include the high oxygen content of blood in the vein component, the presence of arterial insufficiency distal to the fistula, mild local edema is found, about 50 per cent of the patients show increase in blood volume, and there is marked slowing of the pulse with application of the blood pressure cuff to obliterate the aneurysm (Branham's sign) This phenomenon differentiates the arteriovenous fistula from the arterial aneurysm It is noted that the bradycardia does not occur if the vagus influence is removed by giving atropine These investigators hold that tissue needs, not venous return, determine the increase in cardiac output Furthermore, they find no relationship between heart size and total volume

The relation of the altered physiology and pathology in an arteriovenous aneurysm furnish the foundation for the principles of surgical intervention Delay in the definitive therapy is advisable unless some drastic complication such as hemorrhage or early gangrene supervenes Delay of three to six months enables the establishment of efficient collateral circulation, the absorption of the hematoma, the subsidence of infection and the healing and possible decrease in size of the fistula The presence of vasospasm which may interfere with collateral circulation can be minimized by the removal of the sympathetic pathway by procaine injections or sympathectomy

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Chapter IV

CIRCULATORY DISTURBANCES IN SURGERY

SURGICAL SHOCK

DEFINITION

SURGICAL shock (synonym, traumatic shock) may be described as a disturbance resulting from trauma, characterized by profound depression of the circulation, rapid, shallow breathing, more or less sensory and motor paralysis of the nervous system, and often lowered body temperature The essential physiological features of shock are well formulated in the useful definition given by Moon "Shock is a circulatory deficiency, neither cardiac nor vasomotor in origin, characterized by decreased blood volume, decreased cardiac output (volume flow) and increased concentration of the blood"

Other Types of "Shock" · A great deal of confusion arises from the many totally different senses in which the word shock is used In general, the term refers merely to a group of symptoms The basic feature common to most of the conditions to which it is applied is acute noncongestive circulatory failure This type of failure may be produced when the *propulsive force* is deficient, or when the *distributive apparatus* is deficient, or both As suggested by S C Harvey, instances of the former might well be termed "cardiac failure," and instances of the latter be termed "vascular failure," the causative factor, if known, being added to the designation in each case The term shock could then be abolished altogether

For clarity we must mention certain types of "shock" which are *not* under discussion at present Four types which seldom cause any confusion because they are easily distinguished from traumatic shock will be mentioned first

1 *Shell shock* is a neuropsychiatric condition which is not readily confused with surgical shock

2 *Spinal shock* is the temporary depression or absence of spinal reflexes below the level of a sudden trans-section of the spinal cord in animals or man

3 *Gravity shock* is the state of collapse which can be induced in certain animals (rabbit, snake) by merely holding them in the vertical

head up position it is due to poor vasomotor tone which permits pooling of blood in the dependent parts and thus leads to anemia of the brain

4 *Anaphylactic shock* is an untoward reaction to a foreign substance introduced into the body, following previous sensitization resulting from administration of the same substance

Three further types of "shock" continually cause serious confusion both in the discussion and in the clinical management of surgical shock

5 *Toxic shock* is a state of collapse induced by exogenous or endogenous poisons, the location and nature of the noxious effects differing with different poisons For example, profound circulatory collapse may result from cyanide poisoning or from an overdose of insulin If the patient is said in each case to be in "shock," it is obvious that the term is used in a loose sense and does not imply that the physiological disturbances are identical in the two conditions "Shock" as applied to these and to innumerable other toxic conditions has nothing whatever to do with surgical shock

6 *Anesthetic shock* is a term sometimes used to describe serious immediate collapse resulting from the administration of an overdose of an anesthetic, either general or local Such a condition is obviously the direct result of the specific toxic effect of the drug used, that is, it is a particular variety of "toxic shock," and has no direct relation to surgical shock. The pharmacological effects differ widely according to the nature of the anesthetic, and there is only a superficial resemblance between the clinical syndromes in different instances, mainly because of the common factor of ultimate circulatory collapse in all cases The chief site of action of the different anesthetics varies, thus, ether affects mainly the respiratory center, chloroform seriously depresses the heart while intraspinal novocaine interferes with the functions of the vasomotor system It is apparent that the single term "anesthetic shock" does not express adequately the diverse mechanisms involved, it also suggests incorrectly that surgical shock, which is an entirely different condition, is necessarily a part of the picture

It is true that the very prolonged administration of a general anesthetic can and does lead to the development of real surgical shock. The condition thus produced may be considered anesthetic shock in the true sense and is quite distinct from the immediate and specific toxic effects of the drug It is surgical shock whose chief predisposing cause is anesthesia

7 *Hemorrhagic shock* is a term involving peculiar difficulties in the present connection The profound circulatory collapse immediately fol

lowing massive blood loss forms a striking picture to which the term shock is commonly applied in clinical usage It cannot be emphasized too strongly that the state of collapse resulting immediately from severe hemorrhage is shock only in the loose or "clinical" sense of the word, meaning any condition of profound circulatory depression without reference to the cause, it is not true surgical shock In such a case the patient is suffering from hemorrhage and not from shock Everyone realizes that loss of blood is the one essential cause of the syndrome and that the very prompt transfusion of a volume of blood corresponding to the amount lost quickly and completely cures the condition providing there is no further bleeding The beneficial effect of transfusion upon true traumatic shock, on the contrary, is not at all as certain and predictable and it is well known that in spite of ample blood transfusions death may result Obviously, therefore, the two conditions are not identical It is true that they are often present together, but many cases of surgical shock are unassociated with any hemorrhage, large or small, and it is well to consider only this type of case in the present discussion in order to avoid confusing the effects of hemorrhage with the phenomena really due to shock

PRIMARY SHOCK

Surgical or traumatic shock is classified as primary and secondary Primary shock is the state of collapse which develops immediately after some severe injury or after the sudden onset of some serious pathological change, such as perforation of a peptic ulcer. The mechanism which produces the condition is not fully understood but, since it develops very rapidly, probably it is largely, if not exclusively, of nervous and neuropsychic origin Strong noxious afferent impulses set up in the injured region travel to the central nervous system and there cause marked disturbances in the functioning of the centers which control the circulation Coincident subjective factors such as pain and anxiety probably aggravate the depressing effect upon these centers by reason of nerve impulses passing from higher cerebral centers to the medulla The principal effect appears to be inhibition of the tone of the smaller vessels, thereby increasing the capacity of the vascular system There is consequently a relatively inadequate amount of blood, the blood pressure falls and the pulsations of the heart become feeble but increase in frequency in an effort to maintain the normal minute output The circulatory depression leads to secondary disturbances in other systems, so that the whole clinical picture is indistinguishable from that of secondary shock Certain blood changes, however, which are an essen-

tial element in the latter condition (see below) are absent in primary shock the blood remaining normal

If the etiological factor is not too severe or is soon removed, there is usually quite rapid recovery from primary shock within a few hours, but under less favorable circumstances it persists and secondary or "true" shock develops and supplants it The transition from one to the other is insidious in that the prominent clinical features of the two states are identical The event can be detected directly only by examination of the blood for changes characteristic of secondary shock These may be obscured by complicating factors such as hemorrhage From the practical standpoint, however, it is not necessary to distinguish minutely between primary and secondary shock by either physical examination or laboratory methods because the status of a given case can usually be inferred with sufficient accuracy from the history, and the finer distinctions have no bearing whatever upon therapy

Primary shock then resembles somewhat the common fainting attack in the sense that it is a disorganization of the integrated action of the cardio-vascular system, is nervous in origin, and has a natural tendency toward recovery It differs from ordinary syncope (which is often purely psychic in origin and largely due to vagal slowing of the heart) in that it is initiated by some real trauma or other organic change, the vascular disturbance (inhibition) predominates over the cardiac, the duration is greater and there may be secondary effects upon other systems

It is stated that primary shock is sometimes promptly fatal, even without the development of secondary shock and in the absence of any demonstrable organic change which of itself could be considered a competent cause of death. If so, the occurrence is extremely rare and for all practical purposes its possibility may be disregarded

Infrequency of Primary Shock Primary shock is not a common condition It is much rarer than was formerly believed In many instances of immediate post traumatic collapse attributed to primary shock, the condition is probably due to associated hemorrhage At any rate most cases of primary shock are associated with wounds which are very serious and extensive or with which considerable hemorrhage is associated Certainly in the case of fracture of the leg bones so frequently encountered whether simple or compound, it is unusual to observe a really marked circulatory collapse, in fact when the latter occurs early one is inclined to seek for some coincident injury to explain it such as rupture of a viscus with internal bleeding or fracture of the skull The perforation of a peptic ulcer is commonly said to

induce primary shock immediately, but this is not borne out by closer observation of the state of the circulation, which really is not disturbed markedly

Operative Trauma and Primary Shock. Phemister and Livingstone found that even prolonged operations on the extremities involving chiseling and sawing of bone usually cause little or no circulatory embarrassment if hemostasis is adequate and anesthesia is properly administered It seems that handling of tissues and cutting of bone have been overemphasized as causes of shock It is true that they may cause a prompt fall in blood pressure reflexly if anesthesia is not deep enough to suspend conduction of afferent nerve impulses from the operative field By testing for action currents in afferent nerve fibers it has been shown that nerve impulses are abolished by depths of general anesthesia usually employed in surgery

The treatment of primary shock itself is symptomatic The chief clinical importance of primary shock is as a factor in the production of secondary or "true" shock, and as a warning of the latter The subsequent discussion will refer only to the latter condition

Irreversible Shock: The term "irreversible shock" is difficult to define precisely. Shock following blood loss will usually be corrected by blood transfusions given by vein If, however, shock is profound or is not treated promptly, large amounts of intravenous fluid will not relieve the condition In fact, under these circumstances overloading the venous portion of the circulatory system might produce pulmonary edema and death The exact mechanism of irreversible shock is not understood One important factor in relieving it, however, is to reestablish an adequate flow of blood in the coronary artery at the same time depleted blood volume is restored It is apparent that the myocardium is called upon for increased work during shock

An interesting experimental observation by Fine *et al* has shown that in animals in which the liver is adequately perfused the ability to withstand shock is increased

The prompt use of intra-arterial transfusions of blood will usually reestablish the coronary artery flow and at the same time establish sufficient blood volume It is important, therefore, to employ this method in patients with severe or irreversible shock

SECONDARY SHOCK

Causes of the Symptoms in Shock All the symptoms and signs of true surgical shock can be explained satisfactorily on the basis of *circulatory depression* as the primary event Thus, the pulse rate is

accelerated as a compensatory reaction to the lowered blood pressure Pallor of the skin indicates an attempt to shunt the blood away from the surface of the body so that the impaired circulation will be devoted mainly to supplying the more vital structures, particularly the brain

Rapid, shallow breathing is characteristic of depression of the respiratory center rather than of stimulation The respiratory depression in shock is due to marked anoxemia of the respiratory center caused by deficient blood supply to it. Anoxemia, instead of depressing, stimulates the respiratory center under ordinary conditions, inducing increased ventilation of the lungs But this effect is produced when the *tension* of oxygen in the blood bathing the center is decreased rather than when an inadequate *amount* of oxygen is supplied per minute In shock the latter change predominates Whatever blood reaches the respiratory center is under normal oxygen tension, that is, is thoroughly oxygenated because it has been aerated in the lungs to the usual extent. The trouble lies in the fact that not enough blood passes through the center in a unit of time, hence the amount of oxygen supplied is deficient. As a result the center soon becomes "fatigued" and shallow, rapid breathing results

The subnormal temperature frequently observed in shock can be ascribed partly to lowering of the metabolic rate as a result of the inadequate supply of oxygen to the tissue The blanched appearance and coldness of the skin would not suggest that it is due to an increased rate of heat loss, yet rapid loss of heat is favored by sweating which is usually profuse The sweating is probably an incidental effect of the general sympathetic stimulation in response to lowered blood pressure That combustion processes are curtailed has been confirmed directly by the finding of basal metabolic rates as low as —30 in cases of shock.

A patient in profound shock, though conscious and well oriented because the cerebral circulation is maintained the best, may not feel or respond to noxious stimuli which would cause pain in a normal individual, such as a pin-prick or pinching Likewise, the other senses are depressed and only very strong stimuli are perceived. The patient exhibits depression of voluntary motility in that he refrains from all unnecessary spontaneous movements, and shows marked weakness when he is asked to perform some movement against resistance Depressed reflex control of the muscles is evidenced by the flaccid, atonic condition of the muscles and by diminution or absence of the reflexes All of these effects can be attributed to impaired circulation through the brain and spinal cord, and perhaps also through the peripheral nerves, sense-organs and muscles

Etiology of Surgical Shock: The *predisposing causes* of shock are well known, such as trauma, hemorrhage, infection, dehydration, anaesthesia and exposure to cold The search for the *exciting cause* has been constantly directed toward an explanation of the circulatory disturbances, particularly the lowered blood pressure, since all the other phenomena could well be attributed to depression of the circulation as described above Regardless of the more remote factors which may be involved, lowering of the blood pressure must be in every instance due to a disturbance of the heart, the blood vessels, or the blood, or of several of these elements

The Heart in Shock For a very long time the heart was believed to be at fault in shock, for the rapid thready pulse was taken as a measure of the functional status of the heart Therefore, "cardiac tonics" were administered in shock but without benefit The mechanism by which the etiological factors such as trauma, for instance, might bring about the cardiac depression, was not explained, except for the vague assumption of the transmission of noxious impulses over nerve pathways Later Henderson's acapnia theory held that the heartbeat was rendered ineffective by reason of inadequate relaxation during diastole and hence incomplete filling, the result of a subnormal concentration of carbon dioxide in the blood (acapnia), for it is known that carbon dioxide normally promotes the relaxation phase of the heart cycle The lack of CO_2 was attributed to over-breathing with excessive removal of CO_2, the hyperpnea being the result of pain, hemorrhage, induction stage of anesthesia or other factors associated with the cause of shock in the particular case

Various kinds of evidence have proved, however, that the heart is in good working order in uncomplicated shock When exposed in an experimental animal in which shock has been induced, the heart is found to be beating vigorously in spite of the collapsed state of the peripheral circulation A suitable dose of adrenalin will increase the peripheral resistance even in a shocked animal sufficiently to induce a marked elevation of blood pressure, under these circumstances the heart pumps against the abnormally heavy load very successfully, which would not be the case if inherent weakness of the heart were the primary factor in the circulatory collapse The acapnia theory has been discarded as untenable because there is no overbreathing or other cause for loss of CO_2 in most cases of shock, and there is actually acidosis instead of the alkalosis which would result from loss of CO_2

The Blood Vessels in Shock The blood vessels were next indicted as the cause of the lowered blood pressure in shock The vessels contribute

to maintenance of blood pressure chiefly by virtue of the resistance which they offer to the flow of blood through them Since it is well known that the arterioles are the chief site of this peripheral resistance and are constantly under the control of the vasomotor nervous system, the theory of paralysis of the vasomotor center as the underlying factor in shock was put forward by Mitchell, Morehouse and Keen in 1864 and long after revived and widely propagated by others The center was presumed to be paralysed as the result of the influence of strong noxious nervous impulses reaching it from the site of trauma. The theory seemed to be in accord with many of the observed phenomena, but the therapeutic implications arising from it were not found to be valid That is to say, adrenalin and other vasoconstrictor drugs did not prove beneficial in the treatment of shock Moreover there is direct evidence that the vasomotor explanation is not the correct one Direct inspection of the arterioles in animals in shock and also plethysmographic measurements have shown them to be contracted instead of relaxed and dilated It has been observed in cases of shock in which the pulse is weak or wholly imperceptible that the pulse wave becomes easily palpable after the administration of amyl nitrite, whose principal action is to induce dilatation of the arterioles Moreover the functional integrity of the nervous pathways of vasocontrol in shock has been demonstrated, for active vasomotor responses e g, pressor and depressor reflexes, quite equal to those obtained in the normal animal, can be elicited during shock on the application of appropriate stimuli.

The Blood in Shock As the capillaries contribute much less to the peripheral resistance than the arterioles, it was felt that when it had been shown that the arterioles were not at fault in shock, the blood vessels in general could be ruled out as a cause of the lowered blood pressure

The heart and vessels having thus been presumably found normal, the only remaining circulatory factor was the blood When this was studied carefully the following characteristic alterations were found in shock

1 There is an increased concentration of red cells and of hemoglobin, this increase is much more marked in the skin than in the deeper vessels indicating that the distribution of the blood cells is disturbed

2 The viscosity is correspondingly increased

3 The total circulating blood volume is diminished These findings taken together indicate that some of the fluid portion of the blood has

escaped from the vessels Since it has not escaped outside the body and since accumulations of free fluid are not found in the body cavities, it must have passed into the tissues However, the decrease in the circulating blood volume is found to be relatively greater than the increased concentration of the blood, hence there is an added factor of stagnation or sequestration of some of the blood somewhere in the vascular tree In addition to the oligemia just described it has been found that in shock there is,

4 Moderate acidosis as shown by a decrease in the alkaline reserve of the blood

The above blood findings may be considered the "pathology" of shock

Histamine and Shock Before these blood changes were discovered Dale, Laidlaw and Richards had found (1910) that apparently all the usual clinical features of shock could be induced by the injection of *histamine*, a toxic substance formed on slight chemical alteration of histidine which is an amino acid present in large amounts in all normal tissue proteins Subsequently it was found that histamine, quite unlike other poisons, brought about not only the clinical features but also the pathological alterations in the blood characteristic of shock The suggestion was then made that it, or at least some allied chemical substance, rather than nerve impulses, might be the cause of surgical shock This idea seemed to be supported by experiments performed by Cannon He found that severely traumatizing the limb of an animal did not result in shock as long as the blood supply of the damaged area was obstructed by a tourniquet, but that when the tourniquet was released shock developed rapidly

In order to test the validity of this toxic theory of shock, direct examinations of the blood and tissues of shocked animals for the presence of histamine were made This, however, presents technical difficulties, and the negative findings are not conclusive, for the amounts necessary to induce the syndrome resembling shock are very small Even when histamine is found one cannot be sure that the chemical procedures employed in extracting it from the dead tissues have not caused its formation from histidine or other precursors normally present It is believed that there are traces of histamine or at least "histamine-like substances" present in normal living tissues It is conceivable that the histidine of the body proteins is an ever-present potential source of histamine and may be transformed into the latter when tissues are traumatized, asphyxiated or otherwise disturbed

Assuming for the moment that histamine, formed from tissue

histidine, is the immediate cause of the shock syndrome, how could the various conditions which are recognized as factors predisposing to shock bring about the liberation of histamine? Infection could conceivably give rise to histamine formation by the degradation of tissue proteins which it causes in the affected region Severe hemorrhage necessarily leads to more or less anoxemia of all the tissues, and the resultant interference with the metabolism, if prolonged, may perhaps lead to the formation of histamine A direct toxic action of prolonged anaesthesia upon the tissues causing some degree of chemical disintegration of the latter may be postulated as the source of histamine in shock induced by this means

However, the factors other than physical trauma, such as hemorrhage, infection, anaesthesia, dehydration and exposure to cold may be better understood as predisposing rather than as exciting causes of shock in that they have been found experimentally to increase the susceptibility of animals to the effects of injected histamine For instance if a certain dose of histamine is just large enough to cause death in a certain animal, the animal may succumb from the effects of perhaps one tenth that dose if it is first exposed to an anaesthetic, to cold, or to any of the other factors mentioned above These factors "lower the threshold" for the action of histamine That exposure to cold causes an increase in the concentration of red blood cells is well known As an actual factor in hastening death from hemorrhage or shock, however, Blalock (December, 1934) has shown that its influence is not very great, at least in experimental animals

Whether or not histamine is the cause of shock, the question arises, how does it produce the observed effects upon the circulation which follow its administration? This pharmacological problem was studied experimentally by Dale and Richards, who found that histamine causes contraction of arterioles but paralysis and dilatation of capillaries It does not directly affect the heart to any significant extent. The paralysis and consequent dilatation of the capillaries apparently are responsible for all the other observed changes in histamine poisoning It is found to be a general rule that when capillaries dilate their walls become more permeable Hence loss of fluid from the blood to the tissues occurs, accounting for the concentrated condition of the blood indicated by the increased cell count and increased viscosity When the capacity of the system has been greatly increased by the widening of the capillary bed and when the blood volume itself is diminished as the result of escape of fluid through the too-permeable capillary walls, the volume of blood within the vascular system cannot fill the latter suf

ficiently to maintain the normal level of blood pressure Even though the arterioles are still capable of contracting so as to increase the peripheral resistance, the blood pressure does not rise because the blood stagnates in the huge capillary area just beyond the arteriole and does not return to the heart in sufficient amount to fill the latter adequately for effective pumping action

Histamine Theory of Shock ("Traumatic Toxemia") Since the phenomena of shock are strikingly similar to, if not identical with, the effects of histamine poisoning, it came to be generally believed that shock was caused by the liberation of histamine "or some histamine-like substance" in the body The qualifying clause was necessary in view of the fact that considerable amounts of histamine could not be demonstrated in the blood in cases of shock, and it is quite possible that some other substance or substances might produce effects similar to those of histamine

The sequence of events in shock, according to this theory, may be summarized as follows Histamine, or a histamine-like substance or substances, is formed in and liberated from traumatized tissue This substance is a capillary poison and causes a certain degree of paralysis of the capillaries throughout the body, resulting in dilatation of these vessels The capacity of the vascular system is thereby increased to such an extent that there is a disproportion between the capacity of the system and the amount of blood available to fill it, in spite of a compensatory constriction of the arterioles, for the latter are far less numerous than the capillaries The blood pressure falls as a result of this disproportion, or more specifically, because the blood naturally stagnates in the widened capillary bed and so does not return to the heart fast enough to allow the latter to pump it into the arteries at the normal rate There is thus a diminished circulating blood volume, even if the total volume of blood in the vessels were to remain unaltered Since, however, the walls of the dilated capillaries are more permeable than those of normal capillaries, they permit loss of some of the fluid portion of the blood to the tissues, with the result that the total blood volume is decreased, this is a second and distinct cause of the disproportion between capacity and volume and therefore of the lowered blood pressure

It might be expected that only water and salts would be lost from the vessels, but the increase in vascular permeability is such that the plasma as a whole escapes These changes in the capillary wall eventually become irreversible In the most serious cases, therefore, the giving of even colloid materials, including blood, may be ineffectual in

restoring blood volume The diminished volume of blood circulating per minute means deficient supply of oxygen to all the tissues resulting in numerous secondary disturbances of function, particularly of the respiratory and nervous systems, incomplete oxidation leads to accumulation of acid products of metabolism and accounts for the decreased alkaline reserve (acidosis)

Cannon, whose work was chiefly responsible for the widespread acceptance of the foregoing theory of "traumatic toxemia" for the explanation of shock, had on the basis of experimental evidence excluded the conception, previously favored, of a widespread effect on the organism due to nervous impulses aroused by trauma It had been postulated that such impulses, on passing to the central nervous system, affect it so as to produce profound depression of the nerve cells He found that on severing all the nerves to a limb and then traumatizing the denervated muscles, events occurred quite similar to those seen after trauma when the nerves were intact It is clear, therefore, that there is no essential relation between the production of shock and an excessive stimulation of the central nervous system

Evidence Against the Histamine Theory Both positive and negative evidence has been adduced to refute the histamine toxic theory Negative evidence has been the failure to isolate significant amounts of histamine from the blood or injured tissues or to induce shock in an uninjured animal by the introduction of blood from an animal in shock by transfusion or by cross-circulation experiments Positive evidence of the non toxic origin of shock is the fact that trauma to an extremity in which the arterial blood supply is unimpeded but the veins and lymphatics are completely occluded can produce shock under these circumstances there is no possibility of any toxic substance gaining access to the general circulation Releasing the vein following the trauma does not accelerate the fall in blood pressure The fact that the injection of large amounts of histamine into the limb does not affect the blood pressure proves the completeness of the venous occlusion It is true that massage of a traumatized limb with circulation unobstructed causes a temporary fall in blood pressure but a similar though less marked fall occurs after massage of the normal limb The depressor effect of massage of the traumatized limb may well be due to the production of increased bleeding or *exudation* rather than to the dislodging of toxic material The intestines in animals subjected to trauma to an extremity show no congestion, hence there is no indication of a general capillary dilatation such as would be produced by absorbed histamine Shock is quite easily produced by trauma to large

masses of muscle but is rather difficult to produce by intestinal manipulation

Decrease of Blood Volume in Shock It was recognized by Cannon that, inasmuch as there is always a considerable swelling of the injured region, the fall of pressure might be regarded as due to loss of blood and lymph into the damaged region He tested this suggestion by removing post mortem, with symmetrical cuts, the two hind legs, one normal, the other injured, and weighing them He was satisfied that the difference in weight, which in some instances was only 10 per cent of the estimated total blood volume, but greater in other instances, would not represent enough extravasated blood to account for the fall of blood pressure, though any blood loss might, of course, play a rôle in the development of low blood pressure

Local Loss of Plasma The measuring of the amount of extravasation in a traumatized area has assumed great importance in the experimental study of shock, and conclusions on this point just opposite to those of Cannon are now generally accepted Blalock (June, 1930) found that trauma to the thigh results in some extravasation in the groin and flank, hence this blood is not in the amputated limb when incision is made across the upper part of the thigh He also found Cannon's experiment inaccurate on the ground that the irregular contour of the thigh and the thick muscles at the site of incision make it impossible to be sure that the level of amputation is the same on both sides He eliminated these sources of error by performing amputation in the mid-abdominal region after removal of the viscera and then separating the two limbs by a suitable incision in the midline of the body In control experiments the weights of the two sides were practically the same When low blood pressure was produced by trauma to one of the extremities, the difference in weight amounted to at least 4 per cent of the total body weight, that is, to almost 50 per cent of the total blood volume The blood pressure did not fall to a shock level without the loss of enough blood volume locally to account for the fall

The increased concentration of red cells and hemoglobin in shock is due mainly to the fact that the fluid lost from the capillaries at the site of injury is chiefly plasma, for this fluid on examination is found to contain less hemoglobin than whole blood Soon after trauma, the extravasated fluid contains a high percentage of hemoglobin, later the hemoglobin concentration is less Since there is little tendency for fluid to pass from the uninjured tissues into the blood stream to compensate for the fluid lost locally, the latter represents an actual depletion of the

circulating blood volume and not fluid withdrawn from reserves in other parts of the body

It was found by Wood and Blalock that marked degrees of hemoconcentration (without concomitant alterations in blood volume) are well tolerated in dogs for periods up to 10 days even when the blood hematocrit is 70 per cent and the red blood cell count 10 million per cubic centimeter The effects however, are variable and higher concentrations are definitely harmful or even fatal Blood viscosity increases with the red cell count, but in greater proportion An increase in hematocrit from 50 to 70 doubles the viscosity and a further increase from 70 to 82 doubles it again It would appear then that in shock it is not hemoconcentration but decrease of blood volume that has the deleterious effect

Local Loss of Fluid in Intestinal Trauma In experimental shock induced by trauma to the intestines Blalock (February, 1931) found that the local loss of fluid from the injured bowel into the peritoneal cavity and also into the wall and lumen of the intestine itself was great enough to account for the decrease in blood pressure It amounted to about half the calculated total blood volume, over 4 per cent of the body weight The fluid lost contained a relatively small percentage of red cells The hemoglobin concentration of the blood remaining in circulation increased markedly as a rule, the average increase being about 38 per cent The few experiments in which there was only a relatively small increase in the concentration of hemoglobin are probably explained on the basis of marked stagnation of blood in the capillaries of the traumatized bowel rather than transudation of plasma from them

In the circulatory disturbance produced by histamine the blood pressure declines first, the decrease in heart output occurring later Trauma causes a decreased heart output and later a decrease in blood pressure The changes after hemorrhage have this same sequence Very severe and prolonged trauma much greater than is associated with any operation on the intestinal tract, is necessary for the experimental production of low blood pressure by intestinal manipulation

That the fluid which escapes from the blood stream after trauma to an extremity or to the intestines has approximately the same composition as blood plasma has been shown by Beard and Blalock Its high protein content indicates markedly increased permeability and hence severe damage of the capillaries in the traumatized tissues This loss of plasma proteins at the site of injury is probably the most important factor in the production of traumatic shock Inasmuch as the fluid has

an osmotic pressure about equal to that of blood, once it has escaped from the vessels it resists absorption Johnson and Blalock found that the loss of plasma from the blood stream is more harmful than the loss of a corresponding amount of whole blood or of red cells One reason for this is probably the fact that the osmotic pressure of the circulating blood is lowered more by the loss of plasma than by the loss of an equal amount of whole blood or of red cells, for the cells of the blood do not contribute to its osmotic pressure

Plasma Potassium in Shock Plasma potassium concentration is normally quite constant, ranging between 13 3 and 25 milligrams per 100 cubic centimeters, which is equivalent to 3 3 to 6 5 milliequivalents per liter Zwemer and Scudder report that in experimental shock produced in cats by trauma, failure of the mechanism regulating plasma potassium is evidenced by fluctuations in the potassium concentrations followed by a rise to a high level This change is part of the alarm reaction

When blood stands for some time the potassium content of the plasma increases from diffusion of potassium out of the red cells In man the erythrocytes contain 20 times as much potassium as the plasma. Blood preserved for 30 days by the methods generally in use may contain 100 milligrams of potassium in each 100 cubic centimeters of plasma Scudder (1940), from studies on animals, concluded that it would probably require the rapid transfusion of three to five liters of such altered blood in man to cause death by the excess of plasma potassium This author states, however, that in shock, wide fluctuations in the patient's plasma potassium concentration carry an unfavorable prognosis He stresses the importance of rise in plasma potassium, referring to it as the "one common denominator in the phenomena of shock" Many other observers, however, attach no significance to plasma potassium changes in shock, and view them as one of the incidental effects of the condition Scudder suggests that the benefit of gastric lavage or suction in minimizing shock in intestinal obstruction may be attributable to removal of potassium from the body He does not refer to this procedure, however, in connection with ordinary traumatic shock

To explain why shock due to trauma is usually more difficult to treat than circulatory collapse due to uncomplicated hemorrhage, it has been pointed out by Harris and Blalock that after trauma any procedure that increases the hydrostatic pressure in the blood vessels tends to cause further loss of fluids through the injured capillaries In shock there is presumably the same tendency for tissue fluid to pass into the blood in the uninjured regions as in decreased capillary pressure due to hemor-

rhage But this accession of fluid from the normal tissues, if it occurs, probably leads to further loss of fluid in the injured area It has been shown that the fluid absorbed from the tissue spaces by the blood contains no protein There is some evidence that the normal tissues fail to contribute appreciable amounts of fluid to the blood stream in shock, for tissue analyses fail to reveal any appreciable decrease in the water content of the uninjured tissues after either trauma or hemorrhage

Generalized Capillary Anoxemia in Shock When the general circulation remains seriously impaired for a number of hours as a result of severe hemorrhage, treatment is no longer as effective as it is in the early stages of the condition General injury of capillaries results when there is an insufficient flow of blood from any cause It is reasonable to suppose that as a result of the deficient circulation in which all the tissues suffer from some degree of anoxemia, the functional integrity of the capillaries throughout the body becomes impaired because of an inadequate supply of oxygen This would lead to relaxation and increased permeability of all the capillaries and may well explain the poor response to therapy when circulatory depression due to hemorrhage has persisted for some time Loss of fluid through capillaries thus damaged by anoxemia probably explains also the increased concentration of red blood cells and hemoglobin which develops under these circumstances, replacing the diluted condition of the blood which is present earlier in hemorrhage

A similar sequence of events doubtless occurs in traumatic shock Once the circulation as a whole has become depressed as a result of capillary injury at the site of the trauma, the capillaries throughout the rest of the body are subjected to more or less anoxemia, and suffer progressive impairment of function evidenced by lessened tone and increased permeability Then loss of plasma from the blood occurs not only in the injured area but throughout the body, this explains the unsatisfactory response to treatment

Tourniquets and Shock Phemister and Livingstone studied the effect on the blood pressure of releasing the tourniquet after constriction of a limb has been maintained during an operation In 76 cases in which the average constriction period was 75 minutes, there was a temporary fall in blood pressure of slight or moderate degree in 63 cases, and a marked fall in seven cases, no change in blood pressure occurred in the remaining six cases These data support the generally accepted view that releasing a tourniquet after it has maintained constriction for a considerable period is followed by some decline in blood pressure There is no

general agreement as to the explanation of this effect and some experimental studies have failed to show that it occurs at all It seems reasonable to suppose that the period of anoxemia of the limb damages the capillaries slightly so that when the blood supply is restored the capacity of the vascular system in the part is greater than normal by reason of dilatation of the capillaries The asphyxiated capillaries may also permit the escape of fluid into the tissues

The application of a tight tourniquet to the hind limb in the dog not including the artery has little or no effect on the blood pressure Such a tourniquet applied to both hind limbs however causes the mean blood pressure to fall to about 70 millimeters mercury, even without the application of any trauma If the tourniquet is applied to one limb (the artery being free) and allowed to maintain constriction for a considerable time, its removal will then be followed by a fall in blood pressure

If low blood pressure, produced experimentally by whatever means, such as cardiac tamponade, administration of acetylcholine etc, is maintained for some time, a marked increase in concentration of red blood cells occurs The loss of plasma from the blood under these conditions probably is attributable to a leaky condition of all the capillaries as a result of anoxemia damaging their endothelium

The Present Understanding of Shock In summary, the present conception of the mechanism of traumatic shock is as follows Damaged capillaries in the injured area permit the escape of fluid, partly whole blood but chiefly plasma, from the circulation in amounts sufficient to produce a considerable decrease in the circulating blood volume The resultant impairment of the circulation as a whole leads to some degree of anoxemia throughout the body The anoxemia damages the capillaries everywhere so that there are dilatation and increased permeability of capillaries in all the tissues, this means the combination of a factor which increases the capacity of the vascular system with a factor which reduces the volume of blood These changes permit stagnation of blood and further loss of circulating fluid from the vessels, and thereby aggravate the impairment of circulation and general anoxemia If the latter persists for some time the damage to the capillaries becomes irreparable.

This conception of shock, though differing radically from the capillary toxemia theory formerly held, involves nevertheless a basic feature of the latter, namely generalized damage to capillaries, with loss of blood from circulation but not from the body In the present theory this damage is attributed to a non-specific factor, namely anoxemia, whereas in the histamine theory it is attributed to a specific toxic sub-

stance The therapeutic implications of the two theories are about the same

'Generalized Inflammatory Hyperemia" Theory In substantial agreement with the conception of shock given above must be mentioned that of Moon, which however differs with regard to the mechanism responsible for the generalized capillary damage Moon bases his hypothesis on the work of Lewis and other students of capillary physiology who have shown that *metabolic substances* discharged from tissue cells cause dilatation and increased permeability of capillaries with which they come in contact These substances are liberated either by functional activity of the cells, or by injury of any kind to the cells in the one instance they initiate functional hyperemia, in the other, *inflammatory hyperemia* It is postulated that when the circulation of blood to a large portion of the body is impaired, or when there is extensive injury to tissues these substances are liberated in excessive amount and by their very widespread action upon the capillaries throughout the body produce those adverse effects upon the systemic circulation which precipitate the syndrome known as shock It is emphasized that such effects are merely an enormous exaggeration of the normal physiologic purpose which these substances serve and that the substances cannot accurately be designated as "toxic" in nature, since they are really hormonal substances, by which damaged tissues bring aid to themselves

Moon found no exception to the generalization of Ebbecke (1917) that those agents which cause a wheal—"the triple response"—when applied to the skin, will cause the shock syndrome if their effects are produced systemically He believes that these phenomena are manifestations of identical physiological reactions, the one in a local area and the other in extensive visceral or systemic areas, that the difference between them is quantitative not qualitative, that the wheal is shock in miniature He emphasizes the fact that the post mortem features of shock (congestion of mucous and serous membranes, with ecchymoses) are indistinguishable from those of asphyxia, anaphylaxis, burns, peritonitis, and a number of other conditions, and believes this strongly suggests similar causative mechanisms Less significance is attached to this pathological evidence by others however The characteristic visceral congestion in shock is considered by Moon to be active congestion, because passive congestion, regardless of its origin, produces engorgement of the spleen, whereas in shock the spleen is relatively bloodless

In several respects the accepted explanation of shock seems defective though the deficiency may be only apparent The "lost" blood, which is

presumably stagnating in the capillaries, has not been satisfactorily located The usual pallor or only faint cyanosis of the skin indicates that very little of it is in or near the integument Examination of the viscera does not seem to reveal enough congestion in the splanchnic region to account for the amount of blood that has disappeared from circulation after allowance is made for the loss of plasma from the vessels It has been suggested that the skeletal muscles retain the greater portion of the lost blood Though conclusive quantitative evidence on this point has not been produced, this explanation seems plausible when it is realized that skeletal muscle constitutes a large portion of the entire body, estimated at nearly 50 per cent by volume, and is conspicuously rich in capillary networks In man the venous cistern formed by the large veins of the chest and abdomen has a capacity of only about 450 cubic centimeters It has not been shown to play any rôle in the sequestration of blood in shock

The failure of edema to develop as a result of the transudation of fluid from the blood vessels into the tissues is readily understood when the quantity of fluid concerned is considered The total volume of blood in the body is about 5 liters, about half of which is fluid and half cells Even if all the fluid were removed from the blood and distributed among the tissues, which is an impossible extreme, it would increase their volume only about 3 per cent, whereas the fluid content of the tissues must increase by about 10 per cent before edema is detectable clinically

It is commonly observed that an equal degree of shock does not always follow injuries of the same severity One patient may develop profound shock in consequence of an injury of rather moderate severity, whereas another patient who is subjected to much more severe trauma may show little evidence of shock A great many local and general factors may well account for this apparent inconsistency The tissue damage itself, though seemingly equal in the two cases, may possibly be different in some important respect The susceptibility of the individual will vary according to such general factors as age, physical condition and the presence or absence of hemorrhage, infection, dehydration, etc Aside from these influences, there is a large individual variation This unknown factor should always be given consideration

The very exceptional instances in which death follows trauma in which there is no hemorrhage and no gross muscle injury cannot be explained on the basis of traumatic shock This applies to deaths following operations of only moderate magnitude Even in non-fatal cases of so-called postoperative shock, there is often reasonable certainty that there has not been enough loss of blood volume either by hemorrhage

or by transudation into injured tissues to account for the circulatory collapse In such instances the collapse must be due to other factors such as anesthesia, anoxemia, toxemia, etc , and it is not really a state of shock, though it is commonly so called

Measurement of Shock *The Blood Pressure* The degree of reduction of blood pressure was for a long time regarded as a fairly accurate index of the degree of shock present However this criterion has distinct limitations for in the early or developing stage of shock the arterial pressure may be maintained at a normal level for a time, even when a serious diminution of blood flow has already set in During this state some of the clinical features of shock may be present such as weakness, pallor and sweating The blood pressure is maintained at this time largely by reason of strong over-activity of the vaso-constrictor center If the contraction of the arterioles is of maximum degree, one of the compensatory mechanisms for maintaining blood pressure is already expended and the defense against the disturbing factors incident to an operation is correspondingly weakened Any unfavorable factor such as the occurrence of even a slight hemorrhage or the administration of an anaesthetic may then cause the blood pressure to fall very low

Blood Flow in Shock The volume of blood flowing through the tissues per unit time is the factor of fundamental importance in the circulation As a result of diminution in total blood volume, whether in hemorrhage or shock, the percentage decrease in the volume flow of blood per minute far exceeds the percentage decrease in the total blood volume The volume flow may be reduced as much as 85 per cent in some regions with little or no change in general blood pressure It is apparent, therefore, that the blood pressure may fail to indicate the gravity of the circulatory disturbance The circulation may be already seriously impaired before there is any significant change in systolic blood pressure The minute output of the heart falls 30 to 50 per cent before there is any marked fall in blood pressure Therapy therefore should not be delayed until the blood pressure is definitely below normal The blood pressure is an inadequate guide to the state of the circulation in shock, even when combined with the pulse frequency and amplitude These factors reflect merely the momentary condition of the circulation rather than its functional capacity, as Rehn mentions in stressing the importance of the quantitative aspect of postoperative circulatory disturbances

The product of the minute volume flow of blood and the red cell count may be regarded as the 'nutrient flow' with respect to oxygen supply When the nutrient flow is reduced the injection even of an inert solu

tion such as normal saline increases it because the solution (by increasing total blood volume) raises the minute volume much more than it dilutes the red cells

Because of its convenience, however, determination of the blood pressure gives information of some value, providing it is borne in mind that low blood pressure is not a sign of the developmental stage of shock but of decompensation In a wounded individual a systolic pressure which remains persistently below 100 and a diastolic pressure below 65 are indicative of danger of serious shock Systolic pressure has to be maintained at 90 millimeters mercury at least if an insufficient blood supply to the contracting mechanism of the heart is to be avoided In fully developed shock the determination of the arterial pressure is often difficult and it may be impossible to determine the diastolic pressure

Hemoconcentration in Shock Very great stress is laid upon hemoconcentration as a diagnostic and prognostic feature of shock by Moon, who is convinced that it is the earliest detectable manifestation of shock as well as the most accurate index of its severity He believes it has an enormous potential value which is not generally comprehended, and describes it as a feature which appears early, is regularly present, progresses parallel with the circulatory deficiency and is detectable by simple means Of the four methods of recognizing hemoconcentration which he has used—hematocrit readings, specific gravity of the blood, hemoglobin content and erythrocyte count—he finds the erythrocyte count the simplest and most accurate He calls attention to the fact that a slight hemoconcentration usually occurs after any major surgical procedure, varying with the extent and duration of the operation and with the patient's ability to react Moon states that when shock is fully developed, the blood chlorides are below normal and the coagulability of the blood is markedly decreased Drew and his associates emphasize the value of measuring hemoconcentration as a means of controlling the administration of fluids in shock and other clinical conditions

Venous Pressure in Shock The venous pressure is diminished in shock In view of the low venous and arterial pressures in shock and the concentrated state of the blood it is not apparent why fluid does not pass from the tissue spaces into the blood stream, as occurs after hemorrhage Instead the plasma itself is able to escape through the damaged capillary walls

Impairment of the circulation, that is, decreased volume flow of blood per minute, when caused by trauma to the central nervous system is usually accompanied by some fall in blood pressure The fall in blood pressure is not delayed until the volume flow has fallen to a

certain critical level, as in the case of hemorrhage and shock, the changes in blood pressure tend to parallel the other circulatory changes For this reason a fall in blood pressure is not as serious a sign in operations on the central nervous system as in other operations or in hemorrhage

The vasomotor center withstands anoxemia better than any of the other vital medullary centers Even when the blood pressure has already fallen to a low level in shock, vasomotor tone may be well sustained, maintaining considerable constriction of the arterioles Even up to the time of death from shock the arterioles preserve some tone and the vasomotor center some capacity to react The ultimate failure of the center to respond to the stimulus of the low blood pressure is due to the fact that the center itself has become too severely damaged by anoxemia When the vasomotor center has lost its capacity to maintain vascular tone there is no known means of restoring the blood flow to normal The beneficial effect of transfusion is only temporary When therefore in shock this stage has been reached the secondary damage from oxygen lack is too severe to permit recovery

The capillaries are the essential effector organs of the circulatory system, the organs in which the real work of the circulation is done, for the interchange between the flowing stream and the active tissues occurs only in the capillary portion of the circulatory system All the other parts of the system—the heart, arteries and veins—exist merely to provide a continuous flow of blood through the capillaries The effectiveness of the blood as a carrier of food and oxygen depends on the number of trips it makes from loading places to unloading places therefore the speed of the circulation is obviously of great importance in determining the usefulness of the blood in the body

The estimation of the speed of the circulation, though more important unfortunately is not as simple a matter as the determination of the blood pressure And contrary to what might be one's first impression the blood pressure is not a reliable index of the rate of blood flow The latter, as mentioned above, may be much reduced in the early stages of shock when there is as yet no decrease in arterial pressure One might suppose from the blood pressure alone that all parts of the organism are receiving their normal quota of blood, when this is far from being the case A compensatory vaso-constriction operates to shut down the volume flow of blood in the less essential tissues while adequate volume flow is maintained in the essential organs Experimentally it is found that as long as normal arterial pressure is maintained the blood vessels of the central nervous system and of the heart do not

undergo constriction even though in less vital parts such as the skin and salivary glands there may be marked vaso-constriction. The volume flow through the peripheral tissues is diminished more by a reduction of total blood volume than by a reduction of blood pressure, whereas the volume flow through the essential organs such as the heart and central nervous system, on the contrary, is little affected until there is a fall in blood pressure

The reduction in per minute blood flow that precedes insidiously the fall in blood pressure is a disturbing factor of the greatest importance, it paves the way for the decrease in arterial pressure which is the final step in rendering the circulation inefficient This fact is of practical importance Whereas to measure the volume flow of blood is very difficult and cannot be done under ordinary clinical conditions, the blood pressure, which can be readily determined, serves (poorly) as a basis for estimating the degree of impairment of the circulation It should be understood that the blood pressure is only a convenient means of inferring approximately what cannot be measured directly, namely the rate of blood flow

With the same blood pressure level in each condition, shock and hemorrhage differ in that in hemorrhage the volume flow of blood may be more nearly adequate for the tissue needs than in shock, for in hemorrhage fluid passes from the tissues into the blood stream tending to restore the blood volume This apparently does not occur in shock The difference in blood flow in shock and hemorrhage of equal severity as far as blood pressure level is concerned is reflected in the unequal disturbance of the metabolic rate, for in shock the metabolism is considerably reduced whereas in hemorrhage it is only slightly reduced

The cells most sensitive to lack of oxygen are those of the cerebrum and cerebellum, restoration of cerebral function may be impossible after a few minutes of anemia The cells of the medulla are more resistant, being able to withstand anemia for longer periods The spinal cord can probably tolerate interruption of blood supply for 30 minutes, sympathetic ganglia for an hour or more Lack of oxygen is much more harmful than accumulation of CO_2 in abolishing the function of cells deprived of their blood supply The rate of blood flow through the brain seems to be directly dependent on the height of the arterial pressure, and experiments indicate that as the pressure falls the rate of flow falls to a greater degree The anoxemia to which the nerve cells are subjected may therefore be greater than the blood pressure would seem to indicate

Treatment of Shock —The best preventive treatment of traumatic

shock, aside from the prevention as far as possible of all unnecessary trauma, is, (1) to avoid or to minimize and combat the known pre disposing factors already mentioned, hemorrhage, dehydration, etc, and (2) to apply early, in all cases in which shock may be reasonably expected to develop, the same measures that would be employed for its relief if it were already actually present

Application of Heat Bad effects of exposure to cold and great benefit from the application of heat in shock have been very generally acknowl edged for a long time, but it is probable that the factor of environmental temperature has been exaggerated Sometimes extreme measures are taken, at great trouble, to supply external heat Yet it is not entirely certain that the patient in shock, unless his body temperature (not skin temperature) is actually below normal, requires an environmental temperature much above that which is congenial to the healthy individual The coldness of the skin, which has probably been assumed to be a clear indication for heat therapy, is the result of a protective vasoconstriction in compensation for deficient blood volume, and not closely related to impaired temperature regulation Apparent clinical benefit from heat therapy evidenced by recovery of skin warmth is perhaps spurious Certainly any success in elevating the body temperature connotes an increase in the metabolic rate and in the oxygen requirement of the patient this increases correspondingly the task of the already laboring circulatory system

This matter has not been conclusively settled, and has had little accurate study, perhaps because of the widespread conviction that heat is of striking benefit in shock and that this benefit is clinically conspicuous However, Blalock and Mason found that in dogs suffering from shock induced by trauma or hemorrhage, the application of extreme heat (causing a rise in body temperature) diminished the chance of survival and shortened the period of survival, whereas, extreme cold (with a fall in body temperature) had no ill effect. These authors are of the opinion that drastic means to elevate the skin temperature of the patient in shock should not be used

With regard to curative treatment, it is necessary to discriminate between the initiating factor and the sustaining factors in shock. The initiating factor is loss of plasma from damaged capillaries at the site of injury, with resultant decrease in total blood volume The sustaining factors are slowing of the flow of blood (of which low blood pressure is an inaccurate but convenient index) and the disturbances due to it, namely anoxemia of capillary endothelium leading to general capillary dilatation and leakiness, and anoxemia of the brain tending to produce

ultimate paralysis of the vasomotor center An appreciable time interval is required for the development of these secondary derangements, hence the benefit of early treatment for the prevention or correction of the slowing of the blood stream

Treatment of the Capillary Paralysis Since the primary disturbance in the body is paralysis of capillaries (locally by trauma and generally by anoxemia) causing them to dilate and become more permeable, the most direct curative treatment would be the administration of some substance which would constrict the capillaries and render them less permeable Such a substance is not available, for the known substances which constrict capillaries cannot be administered safely in proper concentrations to exert this action on the damaged capillaries, because of other harmful effects which they would produce

Treatment of the Blood Volume Deficiency The capillary dilatation in shock is harmful in that it induces a relative and also an absolute deficiency of blood volume The obvious means of neutralizing this effect of the capillary dilatation is to increase the blood volume by the intravenous injection of fluid, normal saline, for example Saline has no appreciable oxygen-carrying capacity, but there is no particular lack of this property of the blood in shock, in fact, the hemoglobin concentration is above normal and the dilution of the blood from saline injection is a negligible disadvantage The real disadvantage of saline is that it readily and quickly escapes from the dilated capillaries into the tissues and fails to maintain the blood volume for any great length of time, since the capillary walls are abnormally permeable

A colloid solution such as gum acacia is retained longer within the leaky vessels and so is more effective than saline However, serious and even fatal reactions following the intravenous use of gum acacia have been reported by Studdiford and others There is evidence that the substance interferes with the gas interchanges of the red cells, and also that it may cause conglutination of the red cells For days and weeks after the administration of acacia the microscopic appearance of the blood is so altered that a leukocyte count is difficult or may be impossible Blood is the most successful fluid since it contains colloids of the proper kinds and in the correct proportions Transfused whole blood maintains the increase in blood volume longer than any other injected fluid, with the possible exception of blood plasma

Transfusion In some cases of shock associated with infection, transfused blood may also supply some antibodies which will assist in combating the infection In shock associated with hemorrhage the increasing of the oxygen-carrying capacity of the blood by the added red cells

may be of great importance But it should be clearly understood that the hemoglobin supplied is of importance only because of the coincident hemorrhage and is not an appreciable factor in the treatment of uncomplicated shock The transfusion of plasma or serum has been suggested for the treatment of shock and burns Strumia, *et al*, found that citrated plasma, whether fresh or preserved, can be safely transfused in man without cross matching, whereas fresh or preserved serum may cause reactions which are often severe Levinson, *et al*, have preferred serum to plasma because it does not require citrate and is free of fibrin precipitates These advantages of serum over plasma are not generally acknowledged to be of importance

Plasma Transfusion In whole blood transfusions, the plasma plays a greater role than the red cells in bringing about the therapeutic effect in shock However, in most conditions, particularly in hemorrhage, whole blood is superior to plasma Other conditions in which plasma can be employed are severe burns hypoproteinemia from any cause, and conditions calling for the administration of antibodies Preserved blood plasma transfusion has also been found useful in connection with wound healing, general nutrition, water balance, intestinal motility and intestinal obstruction, hemophilia, hemorrhagic disease of the new born, for the reduction of abnormally high cerebrospinal fluid pressure and as a diuretic in nephrosis For reducing intracranial pressure, the plasma is used concentrated to four times the normal concentration This concentrated plasma may cause a marked rise in venous pressure, hence it usually should be given slowly, about 5 cubic centimeters per minute Placental plasma has a higher concentration of proteins than plasma from adult blood Transfusions of whole blood should not be given immediately after plasma transfusion (except type O blood), as the heterogeneous agglutinins injected may cause severe reactions (Mahoney *et al*)

Elliott, *et al* found that plasma obtained from donors who had eaten heartily was unusually cloudy due to the presence of a large amount of fat by using fasting donors the plasma would be relatively free of fat

Convenience of preparation and immediate availability gives plasma some advantage However, transfusions of whole blood are preferable despite apparent hemoconcentration Recent blood volume studies prove the diminution of the red cell mass in most types of shock. Strumia *et al* found it safe to administer plasma at a rate of 10 cubic centimeters per minute either undiluted or diluted one-half with saline-dextrose solution Their average dosage was about 500 cubic centimeters but much larger amounts can be given safely

Concentrated Plasma The use of four times concentrated plasma prepared by desiccation from the frozen state is recommended by Hill, *et al*, for the treatment of shock, hemorrhage, hypoproteinemia and certain cases of general or local edema or disturbance of fluid balance (e g, increased intracranial pressure) In profound shock, they advise an initial dose of 150 to 200 cubic centimeters Most of its beneficial effects are produced by osmotic action, but in addition to this factor, plasma is an ideal food for all cellular protein requirements

In shock there was observed, in general, "an almost invariable, immediate, marked and sustained increase in blood pressure" That the increase in plasma volume is due largely to withdrawal of tissue fluid into the circulation and not merely to the added volume of concentrated plasma is shown by a decrease of specific gravity of the whole blood, although the specific gravity of the added concentrated plasma is much greater than that of whole blood

Whole plasma stored at room temperatures decreases the chance of survival of the virus of hepatitis Dried plasma may be kept at room temperature, is less subject to deterioration or contamination during storage, and may be prepared for administration in a dilute or concentrated solution as desired Harper, *et al*, recommend the addition of 20 grams of dry sterile dextrose to the dry residue of each liter of plasma, as the dextrose serves as a dispersion medium and greatly increases the rate of solubility of the plasma powder They have found sodium sulfathiazole to be a satisfactory preservative Using the hematocrit as a criterion, they found that following plasma transfusion there was an increase in the total plasma volume and a decrease in concentration of the whole blood (dilution of the cellular elements)

There was not a corresponding decrease in concentration of the plasma proteins however The plasma protein concentration generally was not much altered, being sometimes slightly increased and in other cases slightly decreased There seemed to be a tendency for the plasma protein level to rise gradually and slightly over a period of some days following transfusion These observed effects upon the composition of the blood cannot be explained on the basis of simple addition of a known quantity of fluid and of protein to an otherwise unchanging quantity of circulating blood Many factors are involved, some of them not being well understood A portion of the injected protein is quickly lost from the blood stream and simultaneously water is drawn into the circulation from the tissues Furthermore, cellular elements may possibly be called into active circulation, partially compensating for and obscuring the increase in plasma volume that has actually occurred

In some cases the quantity of plasma protein injected was equal to over half the amount of protein calculated to be in the circulating blood before transfusion The slightness of the rise in concentration of plasma protein, or the absence of such rise, can be accounted for only by the assumption that some of the protein had left the blood stream to replenish the reserve or mobilizable fraction of the tissue proteins

Adrenal Cortical Extract A number of observers have reported clinical benefit from the administration of adrenal cortex extracts in traumatic shock However, it cannot be stated that any distinct and consistent benefit has been clearly demonstrated The treatment is based on the fact that, in Addison's disease at least, adrenal cortex extract has a regulatory influence on capillary permeability, restores blood volume, relieves hemoconcentration, raises blood pressure, causes a retention of both sodium and chloride and an excretion of potassium, and increases alkaline reserve through base retention Heuer and Andrus report prolongation of the lives of animals in shock from injection of aqueous extracts of closed intestinal loops, and Wohl, *et al*, of animals with intestinal obstruction, by the administration of adrenal cortical hormone

Grodins and Freeman point out that traumatic shock and adrenocortical insufficiency have the following features in common (1) reduction of blood volume and of blood flow (2) hemoconcentration, (3) increased heart rate, decreased arterial and venous pressure, (4) diminished renal function, low basal metabolic rate, low body temperature, (5) active arteriolar vasoconstriction, (6) increased blood potassium, decreased sodium and chloride, and (7) abnormal sensitivity to cold, anaesthetics, toxins, etc They summarize some of the recent literature on shock

The prime object in the treatment of shock is not to raise the arterial pressure but to increase the *flow* of blood through the capillaries throughout the body, that is, the volume flow per minute This cannot be accomplished by medication The most effective means is to increase the volume of the blood, since loss of blood volume is the cause of the inadequate blood flow The increased arterial pressure readily produced by adrenalin gives a wholly spurious impression of the state of the circulation in the capillaries For it is dependent solely on vasoconstriction and vasoconstriction alone may actually decrease the blood supply to the tissues

In acute hypotensive states resulting from hemorrhage, central vasomotor depression and surgical or nonsurgical trauma recent investigations have indicated the value of a primary amine similar to epinephrine

but differing from it by the absence of a methyl group on the nitrogen atom This amine, known variously as Nor-epinephrine, Arterenol or Levophed, has been studied by catheterization of the right side of the heart Although epinephrine in therapeutic doses may act as an over-all vasodilator and apparently causes hypertension, chiefly by increasing the cardiac output, Arterenol causes over-all vasoconstriction with little or no decrease in cardiac output In hypotensive states it is administered as a constant intravenous drip, diluted 250 times with normal saline or glucose solution By regulating the rate of flow the desired level of blood pressure often can be maintained accurately Occasional cases of hypersensitivity have been reported following administration of the drug, resulting in severe occipital headache, photophobia and stabbing retrosternal and pharyngeal pain Because of its potency patients receiving Arterenol intravenously must be observed constantly by frequent blood pressure determinations and the rate of flow regulated frequently

Shock Position The so-called shock position with the head lowered does not alter the brachial blood pressure Hence it cannot be credited with increasing the general blood pressure It is intended to increase the flow of blood through the brain by raising the pressure within the carotid arteries It is possible for the carotid pressure to increase without a corresponding change in the brachial pressure, but there is no clear evidence that the shock position accomplishes this or is for any other reason preferable to the horizontal position

Oxygen administration is of no great benefit in shock, in spite of the general lack of oxygen in the tissues For the inhaled oxygen reaches only the lungs, which already obtain a satisfactory supply of oxygen from the atmospheric air, it can reach the tissues only through the circulation of the blood Deficient circulation, not oxygen lack, is the basic cause of the tissue anoxia, and oxygen does not improve the circulation

It must be admitted, as Wood, *et al*, state, that there is a prevailing impression that the inhalation of high concentrations of oxygen exerts beneficial effects in the treatment of peripheral circulatory failure These authors reason that since the blood in shock may give up as much as 80 per cent of its oxygen to the tissues (in contrast to a normal 20 per cent utilization), the partial pressure of oxygen in the capillaries would fall from a normal of 35 millimeters mercury to about 14 millimeters mercury, and that the administration of 100 per cent oxygen would be expected to raise it by as much as 50 per cent This reasoning

is inapplicable since it leaves entirely out of account the fundamental cause of the low oxygen pressure in the tissue capillaries, namely the slowness of flow of the blood Oxygen inhalation certainly does not accelerate the blood flow in shock

It should be noted that the abnormally low oxygen tension is in the *tissue capillaries* and that oxygen given by inhalation impinges only on the *lung capillaries* The weak link in shock is the link which joins these two capillary beds, not the link which joins the lung capillaries to the external environment It is true that oxygen inhalation may improve the oxygenation of the lung capillaries above normal and thus cause the slowed blood stream to carry more oxygen per unit of time and Wood, *et al*, cite experimental evidence that this is the case The practical question therefore is a quantitative one Can the oxygenation of the blood in the lungs be increased *enough* above normal in shock to be of clinical benefit? That the increase is not great is shown by the figures given by these authors In hemorrhage shock in dogs the oxygen content of the femoral artery blood was raised by 6 0 per cent, and of the mixed venous blood (right side of the heart) by 10 7 per cent in histamine shock, the oxygen content of the femoral artery blood was raised by 3 9 per cent and of the mixed venous blood by 12 6 per cent, and in traumatic shock the oxygen content of the femoral artery blood was raised by 4 9 per cent The significance of the rise in oxygenation of the venous blood out of proportion to that in the arterial blood is not clear The pertinent fact would appear to be that the arterial blood oxygenation in traumatic shock was raised by only 4 9 per cent This is just what one could anticipate in view of the well established fact that arterial blood becomes about 95 per cent saturated with oxygen on exposure to ordinary atmospheric air (20 per cent oxygen)

In severe shock all types of intravenous therapy may fail to produce more than very transient benefit The fact that injured capillaries continue to allow the escape of plasma regardless of the character of the fluid that is introduced explains the difficulty that is encountered in combating traumatic shock Even when the blood pressure has been restored to normal by transfusion, the damaged state of the capillaries remains for a time at least, and may result in a recurrence of the circulatory collapse The specific defensive reactions which bring about recovery of the capillaries are unknown, but even temporary restoration of blood pressure and blood flow aids immensely (though indirectly) by checking anoxemia of all the tissues including the capillaries them

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Physiological compensations for loss of blood are (1) the processes just mentioned which ultimately restore the *blood* itself to normal, (2) changes in the other circulatory factors (acceleration of the *heart*, constriction of the *blood vessels*) which help to maintain adequate circulation temporarily in spite of the deficiency of blood, and (3) *respiratory* and *renal* activities tending to counteract chemical disturbances resulting from anoxemia

The exact manner in which all these changes are brought about is not clearly known It is not certain just what stimuli produce the various responses, or where the stimuli act The immediate general effects of blood loss are a tendency toward a fall in blood pressure and a deficiency of oxygen throughout the body These two factors probably excite many of the compensatory reactions Thus, decreased pressure within the aorta and carotid sinus constitutes a pressor stimulus as a result of which afferent vagus impulses reach the medulla and cause stimulation of the vasomotor center, of the cardio accelerator center, and probably, of a sympathetic center which controls secretion of adrenalin and contraction of the spleen The relative anemia of the brain consequent upon loss of blood may be sufficiently marked to produce stimulation of these same centers, as well as of the respiratory center causing rapid shallow breathing The actual cause of the prompt intake of fluid from the tissues into the vessels is not apparent. Probably a fall in capillary pressure permits the osmotic pressure of the blood to overcome the ordinary tendency for fluid to diffuse out of the vascular system and to set up a flow in the opposite direction Perhaps slight relative anemia of some or all the body cells alters their water balance in some obscure manner so that they shrink and actively liberate water into the blood vessels Increased manufacture of blood cells is perhaps due to stimulation of the bone marrow by anoxemia The source of the blood proteins in normal health and the mechanisms by which they are restored after hemorrhage are unknown

TREATMENT OF HEMORRHAGE

In the treatment of severe hemorrhage the first indication is to restore the blood volume, for the loss of volume is the largest factor causing decrease of blood pressure and impairment of circulation The oxygen-carrying capacity and the viscosity of the blood are of secondary importance because the amount of oxygen actually required by the individual is relatively small when his activities are reduced to a minimum as they usually are after hemorrhage and blood viscosity is under most circumstances a relatively minor factor in the mainte-

selves Permanently effective restoration of blood volume would seem to require some means of controlling the fluid exchange through capillary walls which is not at present available

The Capillaries as a Vital Organ Since severe shock is a condition which seriously threatens life one might be inclined to consider mere capillary damage as an inadequate explanation for it and to suspect a disturbance of some more "vital" organ, such as the heart or the brain, to be the essential factor in shock It is true that each individual capillary is an inconspicuous structure, but one can imagine that if all the capillaries of all the organs and tissues of the body were removed and rolled up into a bundle they would make a very sizable organ indeed Moreover, it would be a most "vital" organ for the capillaries are the tissue in which the really essential work of the circulation, of respiration, of nutrition and of excretion is performed The capillaries, therefore, are responsible for much more delicate and intricate functions than the heart and, taken together, they constitute a more "vital" organ than the latter

Hawkins (April 1941) has reviewed comprehensively the recent advances in the study and management of shock

HEMORRHAGE

PHYSIOLOGICAL RESPONSES TO HEMORRHAGE

The effect of hemorrhage upon blood pressure varies not only with the amount of blood lost but particularly with the rapidity with which it is lost A loss of 5 cubic centimeters per kilogram of body weight usually causes no fall of blood pressure The fairly rapid loss of 500 cubic centimeters, about 1/8 to 1/10 of the total blood volume, is well tolerated The decreased blood volume is compensated for by immediate constriction of the vessels, so that there is little or no fall in blood pressure Rapid intake of fluid from the tissues soon restores the original *blood volume,* though it decreases the concentration of red cells and hemoglobin If adequate fluids are given the plasma volume is restored to normal within 24 hours even after a large hemorrhage, though the total blood volume remains below normal due to the deficiency of red cells Contraction of the spleen forces reserve red cells into the circulation, and later on the bone marrow manufactures new cells to complete the return to normal *oxygen carrying capacity* Regeneration of red cells is more rapid after anemia produced by destruction of blood within the body than after anemia from external hemorrhage The blood proteins are gradually reformed so as to restore normal *viscosity*

Blood Coagulation There is much uncertainty concerning the physiology of blood coagulation and the spontaneous cessation of hemorrhage Clotting is appreciably hastened by heat Clotting depends upon fibrin, which is formed from plasma fibrinogen (manufactured exclusively by liver) by *some obscure interaction with thrombin* The latter is formed from prothrombin by interaction with the calcium of the blood plasma and with a substance (perhaps cephalin) derived from the platelets or fixed tissues Prothrombin is formed, presumably in the liver, from a fat soluble substance, vitamin K, which is absorbed from the intestinal tract with the necessary assistance of the bile acids Possibly there are antibodies for some of the coagulation factors Attempts are made to supply these various substances by the administration of tissue extracts, platelets, horse serum, cephalin, thrombin, calcium, bile, and vitamin K, the actual effectiveness of these measures is variable

Blood transfusion is often of remarkable benefit in various hemorrhagic diseases It promotes clotting and checks bleeding by supplying some of the substances responsible for normal coagulation of the blood Apparently the mechanism is different in different cases Though the effect is of short duration, it is often useful, as for instance in hemophilia, to diminish the risk of a necessary operation Blood transfusion usually is of help in purpura hemorrhagica and melena neonatorum The latter condition, however, is amenable to vitamin K therapy In hemophilia, though the known coagulation factors are all normal in amount, the coagulation time is lengthened The platelets are qualitatively defective in that they do not disintegrate as easily as normally, yet they disintegrate at the normal rate after washing in saline

Transfusions of blood usually furnish the best method for the treatment of shock. Experiences during the past war established the vast superiority of blood transfusions as compared to blood substitutes in the treatment of traumatic shock Recently, the investigations of Evans and others suggest strongly that blood should be employed in preference to other intravenous fluids in the treatment of burns

Arterial Transfusions In the cases *of severe shock* administrations of compatible blood into an artery has certain advantages Blood pressure levels can be restored quickly and maintained at the desired level by giving the blood at a known established pressure Less blood is necessary to restore blood volume and the danger of overloading the vascular system is less than if large quantities of fluid are given intravenously This method is of particular importance in so-called irreversible shock

nance of circulation Fluid should be given by mouth, by rectum, subcutaneously, or intravenously or by several of these routes When fluid given by mouth and by rectum is absorbed, it is believed to carry with it some colloid material from the gastrointestinal tract into the circulation, for it is found to be retained longer within the vessels and to be more beneficial than fluid given intravenously or subcutaneously However, fluid given intravenously has the advantage of being effective immediately Plain saline restores only the blood volume whereas gum acacia solution raises both volume and viscosity, both factors tending to raise blood pressure In addition gum acacia increases the colloid osmotic pressure of the circulating blood, thus supplying a force which tends to retain the fluid given within the vessels Osmotic pressure acts as an adjuvant in maintaining the prime requisite, blood volume, and has not in itself a direct effect upon the blood pressure

The colloids most often used for restoration of blood volume are blood, plasma and gum acacia One disadvantage of gum acacia solutions is the frequent presence of an excessive amount of calcium Also, fatal liver damage following intravenous use of acacia has been reported (Studdiford) The only advantages of colloid solutions over blood itself are their greater availability and lower cost

These advantages and many others are found in preserved human plasma, either whole plasma, or dried lyophile plasma which can be made up in a solution of desired strength The most outstanding advantage of plasma in the treatment of shock is as a substitute for blood under emergency conditions when whole blood is not immediately available Except in circumstances of war or civilian disaster, modern blood banks will usually make whole blood available

The transfusion of compatible blood overcomes all the ill effects of hemorrhage, restoring the volume, the osmotic pressure, the viscosity and the oxygen-carrying power of the circulating blood Incompatible blood may cause, among other ill effects, the liberation of hemoglobin from red cells, and hemoglobinuria It is said that in passing down the kidney tubules the hemoglobin may be precipitated by the acidity of the urine and in this way cause anuria The characteristic clinical symptom in hemolytic shock of severe lumbar pain has been interpreted by some as the result of spasm of the renal arteries Hesse and Filatov demonstrated in animal experiments and later in a clinical case of hemolytic shock that immediate transfusion with compatible blood relieved the condition Both in the animal experiments and in the clinical case a marked elevation of venous pressure was noted, this phenomenon disappeared after the transfusion of compatible blood

Chapter V

PHYSIOLOGY OF BURNS AND TISSUE REPAIR

Throughout the centuries of recorded medical history, men have concerned themselves with the local treatment of burns The general physiologic derangements incident to thermal trauma, however, have been studied and appreciated only within the last several decades The practical application of this basic physiologic knowledge has resulted in the successful therapeutic management of the scalded or burned patient

The extensive damage and destruction of the body surface produced by heat in any of its several forms is always serious The pathological changes which may occur in nearly every organ of the body are described in standard texts of morbid anatomy The altered physiologic mechanisms accompanying burns and producing the systemic effects of radiant energy are discussed briefly in the following paragraphs

Shock Shock is a constant accompaniment of all severe burns Normal adults with an area of at least 15 per cent and debilitated individuals or children with 8 per cent or more of the body surface burned may be expected to develop shock Since roughly two-thirds of all burn deaths result from untreated or inadequately treated shock, it is a subject of extreme clinical importance The types, phases, and the many etiological agents contributing to shock, as well as the theories pertaining to its origin, are considered in detail in the chapter devoted to the syndrome In general, all modern concepts are based on the reduction in volume of blood returned to the heart along with the proportionately reduced cardiac output A reduced blood volume, toxins, pain, and cold are commonly mentioned as important etiological factors in producing burn shock.

The loss of circulating plasma into and through the burn wound is generally considered the prime etiological factor Edema is characteristic of burn lesions The amount of edema was shown experimentally by Blalock to be sufficient to critically reduce the blood plasma volume The quantity of blood that could be removed from the burned animal before death was small Furthermore, analysis of the tissue edema and blister fluid show them to be plasma like rather than just a watery transudate

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by this patient, and this only after the net loss of 55 pounds of his original body weight "

Serum protein levels which by clinical standards are within normal limits may be found where significant protein depletion actually exists Substantial decreases in the total circulating serum albumin may be accompanied by a significant decline in plasma volume Thus, a normal total protein concentration is maintained. Indeed, normal total protein and albumin levels have been shown to occur in severe hypoproteinism The body attempts to maintain homeostasis of the serum concentration at the expense of tissue protein

Burn Anemia Anemia rapidly develops in the burned patient who survives the initial period of shock The anemia may be so severe that wounds do not heal It is progressive and accompanied by debilitation The true anemia as determined by radioactive measurements of the red cell mass develops in three stages The first stage is initiated by the hemolysis occurring at the time of the acute injury, it is the least severe The second stage is seen in seven to ten days It is in part related to the injury of red cells and depression of the bone marrow The final stage makes its appearance in the third or fourth week It has multiple causes, important among these is wound hemorrhage Between the second and third stages a positive red cell balance may exist for a brief time Gross hemolysis and massive hemoglobinuria may occur in the first hours following a deep burn and are supposedly due to the destruction of the red cells by heat Shen found an increased fragility of the erythrocytes shortly after a bad burn Concerning the other possible explanations for burn anemia Moore states "The administration of large volumes of plasma in the therapy of burn shock could theoretically give rise to destruction of cells if the plasma pools contained an excess of anti A or anti B agglutinins." Erythrocytes may be destroyed at the inflammatory barrier of infected wounds A deposition of iron in this area has been demonstrated Indeed this deposition may be the reason for deviation of iron from the bone marrow Furthermore, toxins of infectious origin may suppress bone marrow activity directly Clinically the anemia may be so masked by the reduction in plasma volume that the red count, hemoglobin, and hematocrit fail to give an accurate measurement of the real deficiency in hemoglobin and erythrocytes

Whole Blood Therapy in Severe Burns *The necessity of intravenous therapy in the treatment of burn shock is well established, but the best fluid to use remains unsettled Evans and Biggers have called attention to the red blood cell deficit present shortly after the burn*

A rapid loss of extracellular fluid from the uninjured parts of the body into the burned area takes place This is first manifest by a reduction in the volume of plasma and later by a reduction in the extravascular extracellular fluid. Since extracellular fluid is mainly a mixture of sodium chloride and sodium bicarbonate, the shift of extracellular fluid into the burned area represents a loss of sodium salts and water by the unburned parts. The water and salt in the cells cannot be drawn upon to mitigate the fall in the volume of the plasma and the volume of the extravascular extracellular fluid and, therefore, the volume of intracellular fluid does not change appreciably

Fox and Keston feel that the tremendous accumulation of sodium in injured tissues is of paramount importance in the reduction of plasma volume On this basis they advocate the use of isotonic sodium solution in the treatment of burn shock The use of human plasma revolutionized burn therapy Today plasma, serum, albumin, whole blood, electrolytes, and glucose are administered

Hypoproteinemia Protein depletion complicates the treatment of any extensive or long standing third degree burn Indeed, whenever 10 per cent or more of the body surface is involved serious nutritional problems result The protein supplied to and retained by such patients is often small, the body reserves are quickly exhausted A serious state of protein deprivation thus rapidly ensues The sources of increased protein demands are numerous Urinary nitrogenous wastes, tissue breakdown, wound exudations, and tissue repair all contribute significantly to protein depletion The increased caloric requirements resulting from fever and infection further magnify the nutritional problem

Protein losses in severely burned individuals have frequently been calculated Taylor presents a detailed study made on the protein metabolism of a patient with 45 per cent of his body area involved in third degree burns He points out, "Nitrogen balance studies based upon urine and stool analyses, together with known nitrogen intake, cannot reveal the considerable nitrogen loss from the burned surface and the demand for building new tissues On a high protein diet alone, this patient developed a protein deficit of 2000 Gm , based upon intake and output studies, which was eliminated and a final, apparent, positive balance obtained In spite of this, the patient's edema increased and it was not until a total nitrogen retention estimated at over 6000 Gm of protein had been obtained that the edema was completely delivered and a good nutrition obtained In other words, at least 6000 Gm of protein were required, over and above that indicated by balance studies

stomach but enters the intestine, it is absorbed and it dilutes the salts of the body The kidneys will not put out this water until an adequate amount of sodium is given Therefore, whether the water drunk be vomited or absorbed it serves always to reduce the strength of the salt water inside and outside of the cells This dilution of the salts of the body is made manifest by falling plasma chloride and sodium concentrations As the salts of the body are diluted by the water, headache, tremors, twitching, blurring of vision, vomiting, diarrhea, disorientation, salivation, and mania appear When the salts are sufficiently diluted convulsions often begin Therefore, it is obvious that salt must be given with the water until the extracellular fluid volume of the uninjured parts has been restored toward normal

Chronic Shock The syndrome of chronic shock has been characterized by Clark 'A reduced total quantity of circulation blood in patients with nutritional deficiency was reported by Chang in 1932 Similar observations in hypoproteinemic animals have been recorded in the reports of the experiments of Holman, Mahoney and Whipple

In a study of patients with persistently unhealed war wounds attention was directed to a syndrome characterized by weight loss, reduced blood volume and increased interstitial fluid volume All of these reports emphasize the coincidence of protein depletion and diminished blood volume The surgically significant feature of reduced blood volume is an increased susceptibility of shock correctible by transfusion replacement of the blood volume deficit." This syndrome serves as a useful guide in the treatment of the chronically burned individual when laboratory data conflicts with clinical studies and observations

Blood Chemical Changes The changes in the chemical composition of the blood following an extensive burn are variable, however, certain general alterations may be noted Peters has written a detailed review of this aspect of burn physiology Plasma sodium rises while the potassium and magnesium content either remains the same or rises slightly Both blood and plasma chlorides fall There is a hyperglycemia immediately following the burn Acidosis has been noted along with a decrease in carbon dioxide combining power and plasma bicarbonate The nonprotein nitrogen is increased Likewise, glutathione amino nitrogen and ammonia occur in greater quantities Hemoglobinemia is seen frequently

Urinary Analysis The volume of urinary output is markedly reduced in every severe and untreated burn Anuria is a constant threat The urinary shutdown has been contributed to shock, renal damage and dehydration Directly it results from a decreased blood flow through the

The validity of this observation is substantiated by the fact that "(1) When intravenous fluid therapy consisted only of plasma, and redeterminations of the total mass of circulating red blood cells were made at intervals during the first 72 to 96 hours, there seemed to be little change in the size of this mass If any change occurred, it was in the direction of a further decrease, and (2) if only plasma was given, and the initial data showed a smaller than normal circulating red cell mass, when the blood volume was returning to normal around the 72nd hour there occurred regularly a moderate to severe secondary anemia, which persisted until red blood cells were given " These workers have rather convincing evidence that whole blood transfusions may be given even if hemoconcentration is demonstrable in the severely burned individual

The effectiveness and value of whole blood transfusions in the initial period of burn treatment, as well as during the later phases, have been attested to by numerous clinical observations Secondary anemia is prevented by the administration of whole blood during the shock phase Plasma protein levels can be maintained at near optimum level A good urinary output is obtained even when hemoconcentration appears marked Toxemia seems less in patients receiving whole blood Healing is perhaps more rapid Intravascular clotting resulting in phlebothrombosis or embolism has not been observed Plasma therapy has, likewise, proven worth while in the treatment of the burned patient Evans and Biggers have cautioned that their observations should not be construed as detracting from the value of this substance in burn management

Burn Toxemia It has been conceded that there is probably more evidence in favor of a toxic element in burn shock than in most other forms of this syndrome The entire subject of burn toxemia and the possible etiological agents and factors is a highly speculative matter Liberated histamine, products derived from tissue necrosis, globulins, altered enzymes, and many other substances have been mentioned as possible toxic agents

Recent experiences have tended to indicate that the early "toxemic" phase of burns is mainly water intoxication and that it can be attributed to permitting the unlimited drinking of water before an adequate amount of salt is given

Early water-intoxication develops following liquid intake Water collects in the stomach and sodium salts are dissolved in it These are subsequently vomited The plasma water that contained the sodium salts is left behind and dilutes the total salt content remaining in the intracellular and intercellular space If the water is not held in the

In Hiroshima secondary burns were numerous They resulted from the spontaneous ignition of clothing or from direct flame contact The blast component of the atomic explosion produced multiple lacerations and numerous fractures which further complicated the treatment of the burn patient by producing additional blood loss, increased shock, and enhancing probability of serious infection

Wound Healing It is a complex phenomenon which envelops basic physiologic and biochemical processes Some of these reactions are so fundamental and so universal that their final nature and mechanism is yet to be discovered Tissue exudates, cellular growth, capillary reactions, protein metabolism, vitamin utilization, enzyme systems, hormone activity, and certain intrinsic factors of specialized tissues are all of major importance

The science of surgery is based primarily upon the ability of tissue to repair itself Every well planned surgical procedure depends largely upon the surgeon's basic understanding of the healing process and his *fundamental knowledge of the transplantation of tissues* *This chapter* considers briefly those factors whose coordinated activities are essential for tissue repair and replacement.

Inflammation and Repair The inflammatory reaction has been declared "the most universal of all pathological processes" It represents the organism's local response to an irritant whether physical, chemical, or bacterial in nature The surgical incision itself is nothing more than a scientifically designed form of body irritant Even the completely aseptic operation invokes of necessity a local inflammatory response In its simpler form inflammation consists of cellular, vascular, and humoral reactions The process is complicated by the division or loss of tissue and by the presence of dead or dying cells In each instance, repair with fibrosis must occur to restore body continuity Nevertheless, *inflammation and repair constitute two separate and* distinct processes. They are frequently associated and may proceed simultaneously in a perfectly integrated manner Either process, however, may be present in the absence of the other Together inflammation and repair represent the body's total reaction to injury

The Effect of Injury on Wound Healing The exact nature of the stimulus for wound healing is unknown Wiesner suggested that injured cells release a substance, a wound hormone, which causes normal cells to proliferate Damaged plant cells were shown by Haverlandt to yield a product which promotes the multiplication of similar viable cells Furthermore tissue cultures in vitro grow more rapidly after be-

glomeruli Isotonic sodium sulfate solutions have been suggested for relief of the anuric state. Urobilin and urobilinogen have been found The specific gravity is increased The reaction is generally acid An acetonuria may exist. Albuminuria is not infrequent and hemoglobinuria occurs Urinary nitrogen excretion has been considered in previous chapters and paragraphs

Hormonal Alterations An imbalance in internal secretions rapidly develops in patients with extensive burns Kieskotten early directed attention to the fact that the outstanding and most characteristic autopsy finding was changes in the adrenal glands Harkins and Long demonstrated a fall in adrenal total cholesterol following scalds, this fall, however, did not occur in hypophysectomized animals Thus, the burn effect on the adrenals may well be indirect and mediated through the pituitary. The use of adrenocortical extract in the treatment of burn shock was advocated on the basis of adrenal damage, its clinical advantage is equivocal More recently ACTH and Cortisone have been used Although the appetite may be increased by ACTH, there is a greater loss of urinary nitrogen Hyperglycemia can occur Furthermore, the mechanism to convert fat into glucose is apparently set into action The immune reaction can be altered The granulating wound appears less edematous and vascular Psychiatric tendencies have developed Whether or not ACTH alters the take of a homograph is not certain Thus, the efficiency of these products in burn therapy awaits further clinical trial Menses may cease following a deep burn, excessive hair growth may develop These changes are associated with an increased excretion of the 17 ketosteroids All of these manifestations can of course be considered as constituting further evidence of adrenal damage

Burns in Atomic Warfare The burn resulting from thermal radiation emanated by the explosion of an atomic bomb is not unlike an ordinary burn, the only significant difference would seem to be the exceedingly short interval of time in which a given quantity of thermal energy is imparted to the skin by an atomic burst as compared to the time required to emit an equal amount of heat by other agents The atomic flash burn results from the absorption of a comparatively large amount of heat in a fraction of a second The damage may be superficial like a sunburn, or deeper as in a second degree burn Full thickness loss of skin results from the absorption of greater amounts of heat The more superficial burns are painful, but heal spontaneously The third degree burns, if at all extensive, require skin grafting

the incision and closure of a surgical wound, a rapid exudation and diapedesis promptly ensue into the defect The fibrin trabeculae in the exudate and clot form the framework for subsequent tissue growth

The phase of fibroplasia begins from three to five days after injury Fibroblasts divide by mitosis and grow into the fibrin network Loeb pointed out that fibroblasts in contact with fibrin strands elongate and grow along the fibrils There is a centrifugal force which directs the fibroblasts towards the central portion of the wound The fibrin network is gradually removed by the fibroblasts and macrophages At the same time capillary buds are formed In a cleanly incised wound, however, little new vascularization is necessary Soon the rapidly increasing fibroblasts and the accompanying blood vessels have filled the defect and restored the continuity of the tissue Finally, epithelial cells proliferate to cover the wound surface

Healing by Second Intention Healing of even a clean wound with loss of substance is a somewhat more complicated affair than that observed following a surgical incision The defect is filled with various tissue exudates, chiefly coagulated plasma, bound together by strands of fibrin The capillaries at the sides and base put forth solid endothelial buds which grow into the mass They unite with one another, become canalized, and fill with blood Thus, a network of capillaries is formed and the exudate becomes vascularized The fibrin, which at first constituted a scaffolding for this new formation, is absorbed by the progressing capillary loops At the same time, connective tissue cells proliferate and become fusiform in shape with vesicular nuclei and branching processes This fibroblastic activity is the most striking feature of the repair process The fibroblasts support the capillaries and permeate the fibrin forming an interlacing network throughout They exhibit a certain degree of polarity which may be altered by mechanical torsion In very young healing tissue the fibroblasts are at first parallel to the sprouting vessels and perpendicular to the surface Deeper down, the tissues being older, they are oblique In the depths of the wound they are parallel to the surface and therefore, perpendicular to the vessels as in the final scar

Granulation tissue quickly covers the floor of the defect owing to the prodigious growth of the new capillaries Fibroblasts subsequently lay down fine connective tissue fibrils between the cells These fibers increase in number and thickness until definite connective tissue can be histologically recognized Even the fibroblasts are compressed between the bundles of new fibers They appear only as thin connective tissue cells consisting of little more than elongated nuclei The capillaries be-

ing traumatized Fischer postulated that a phosphoprotein or nucleoprotein substance was the active stimulating agent Undoubtedly tissue repair in the living organism is stimulated by cellular injury

If a healing factor is produced by damaged cells, it would seem probable that the substance might enter the general circulation and promote healing in other parts of the body Young found that if ten to twelve days following an initial wound a second incision is inflicted on a rabbit's body, the latter wound will heal more rapidly than the first Sandblom likewise, demonstrated this healing promoting phenomenon The impetus is first noted five and a half days after the *primary injury and increases rapidly for several days,* reaching its maximum between the first and fourth week The healing effect disappears six to seven weeks following the initial trauma

The healing curves of the secondary wounds are greater than those of the primary throughout the first 10 days On the fifth day the secondary wounds are 30 to 40 per cent stronger than the initial wounds were at a corresponding time Moreover, there is probably a direct correlation between the extent of the injury and the degree of effect of the healing substance The wound hormone influences both coagulation and fibroplasia

The Healing Process The process of repair is customarily divided into several types for the purpose of study and description The same basic reactions occur in each, it is only in degree that they differ Primary healing, or healing by first intention, occurs in aseptically incised wounds in which the tissues are accurately reapproximated There is no loss of substance and no infection Granulation tissue is minimal Scar formation is negligible Indeed, with perfect approximation in some tissues, such as peripheral nerve, the defect is again bridged by regeneration of the tissue itself

Healing by secondary intention appears in those wounds in which there is an actual loss of substance An unclosed gaping incision, infection, and extensive trauma are among the more common causes for such healing The process is slower and scar formation is prominent

On occasion a wound may be left open at first and subsequently closed When the granulating surfaces are approximated a few days later to hasten healing and lessen the formation of scar tissue, the procedure is known as secondary suture Healing then takes place by third intention

Healing per Primum The primary repair of tissue, when uncomplicated by constitutional deficiencies and metabolic disturbances is largely a problem of tissue chemistry and cellular proliferation After

glands do not regenerate if completely destroyed However, if the deeper portions escape injury there is restoration and reestablishment of continuity with the surface

The liver is the best example of a specialized epithelial derivative with enormous powers of regeneration In experimental animals removal of 75 per cent of the liver is followed by the rapid proliferation of hepatic cells Restoration to normal size occurs within three to four weeks New growth is probably specific, that is, hepatic cells from hepatic cells and bile ducts from bile ducts The salivary glands and the pancreas have much less capacity for reproduction, and destruction is usually followed by cicatrization The excretory epithelium of the kidney, especially that in the proximal convoluted tubules, grows actively following injury, but the highly specialized cells fail to multiply

Adipose tissue is a specially differentiated mesenchymal derivative The formation of fat is usually from pre-existing fat cells In traumatic injury the retained fat is hydrolized and the liberated fatty acids stimulate the production of fibrous tissue To fill a defect, fat cells may occasionally be formed by the metaplasia of fibroblasts

Adult bone does not regenerate but the cells of the periosteum and endosteum retain the capacity to form new bone under adequate stimulation The space between fractured fragments is first filled with a blood clot, then with a fibrous callus, and finally with a bony callus For all practical purposes muscle does not regenerate, but smooth muscle in newly formed vessel walls is a real exception

After division or eruption of a tendon, exudate and blood fill the intervening space A moderately rapid growth of granulation tissue replaces the exudate Soon fibroblastic proliferation into the granulation tissue occurs Shortly the new tissue becomes avascular and takes on the characteristic tendon form The increase in the length of the tendon under such circumstances frequently leads to loss of function When the tendon sheath is also divided, the structures must be carefully sutured or, in all probability, normal healing will not take place, instead scar tissue will form which penetrates into the surrounding structures and results in adhesions

The regenerative potentialities of these and other specialized tissues and organs are considered in their respective chapters The peculiarities of nerve degeneration and regeneration are given in detail Loss of a ganglion cell is irreparable but regeneration of a part of a nerve cell, such as an axon or dendrite, does occur

Infection Infection will be a deterrent to wound healing as long as contaminating bacteria are allowed to multiply and flourish Bacteria

come obliterated and the previously highly vascular granulation tissue is finally transformed into a fibrous, nonvascular mass

The epithelium at the edge of the wound shows signs of early proliferation A thin, bluish white line appears which spreads inward, covering the surface with a layer of young epithelial cells

During the final phase of wound healing there is a generalized contracture of the fibrous tissue The overlying epithelial surface is white, bloodless slightly wrinkled and depressed below the surface The greater the amount of scar tissue, the greater the degree of contracture This contractive and obliterative process continues for an indefinite period, often for months

Brown and Byars have pointed out that a patient with a large full thickness loss of skin usually lapses into one of the following classifications

"1 The large wound may show extreme epithelial activity in the form of piling up of keratin at the margin without progress, or with hopelessly slow extension of the healing edge across the open wound

"2 There may be no epithelial response whatever to the wound stimulus, and, with the continual loss of body fluid and debilitation, death may occur.

"3 The area may heal completely at rest only to break down repeatedly on insignificant trauma or activity of the patient The constant wound stimulus of tension and inflammation sometimes causes excessive keratin formation It is this type of wound which may progress to malignancy, although rarely and at a late date

"4 If even small deep wounds are allowed to remain dirty and if pain is permitted to go uncontrolled, debilitation and death may occur"

Marked disability and permanent deformity are often the result of a full thickness loss of skin The loss of an eyelid may result in blindness An ulcer on the dorsum of a hand may economically incapacitate the patient while an ulcer on the leg or flank may make one bedfast

FACTORS INFLUENCING REPAIR

Intrinsic Qualities of Specialized Tissues A multiplicity of factors contribute to successful wound healing The epithelium covering the surface of the body and lining the hollow viscera, and many of the specialized secretory cells, have great capacity for regeneration after injury The stratum germinativum and the columnar and transitional cells of the gastrointestinal mucosa rapidly proliferate On the cornea, the integrity of the epithelium after a minimal injury may be restored in from six to ten hours The hair follicles, sweat glands, and sebaceous

that "if half of the body surface of a man weighing 70 Kg, and 170 centimeters in height, were to be involved in a burn, the 9,050 square centimeters so involved would lose, according to one rate, 3 8 Gm and according to the other rate, 19 9 Gm of nitrogen in 24 hours Three point eight grams of nitrogen would be 23 75 Gm of protein, or the equivalent of 4,000 cubic centimeters of plasma, or of 114 Gm of meat, and 19 9 Gm of nitrogen would be equivalent to 124 Gm of protein over 20 000 cubic centimeters of plasma and 600 Gm of meat."

The role of protein nutrition in the etiology of the common bed sore has been studied by Mulholland A certain amount of pressure applied with sufficient force and for a significant length of time to a local area of even normal tissue can cause necrosis of that tissue Protein malnutrition, however, so changes the character of the tissues that it takes a smaller amount of pressure exerted by the recumbent body for shorter or longer periods of rest to produce tissue necrosis and the characteristic lesions clinically described as bed sores The excessive loss of nitrogenous products in the urine and from denuded surfaces and the progressive regression in protein concentration indicate that the body protein stores are depleted in the patient with a chronic bed sore

Subnormal serum protein determinations denote body protein deficiency but the converse is not necessarily true Very significant protein depletion may exist in cases where the serum protein level is by all standards normal There are a number of reasons why the blood serum protein level may be completely misleading as a clinical index in the treatment of the large open wound A normal serum protein concentration may occur even when there is a marked decline in the total circulating serum albumin, provided that loss is accompanied by a comparable reduction in the total circulating serum volume

Ravdin suggested that if the means to determine it were available the first effect of protein under nutrition is a reduction in the amount of protein stored in the tissues of the body since every attempt is made to maintain the serum protein concentration at a nearly normal level" Localio found an actual depletion of the fascial protein while the serum protein concentration remained within normal limits

Marked weight loss, fatigability muscular weakness, lassitude, decreased resistance to infection and faulty wound healing are the insidious manifestations of persistent protein starvation, Edema extreme malnutrition, ascites, impaired hepatic function and death are its aftermath

Vitamins Vitamins are essential to many basic physiologic proc

grow and the number of colonies increase unless something is done to starve, remove, or annihilate them Many agents have been advocated to decrease and eradicate bacterial growth, none has been completely successful Frequently, the substances used have proven more lethal to living cells than to the offending bacteria The control of such infections may be fortified by the use of antibiotics and chemotherapeutic agents and by intensifying the immune reactions of the host The eradication of infection depends upon the careful surgical care of the local lesion This necessitates the prevention of contamination Starvation of bacteria is accomplished by the disposal of slough and secretions, and organisms are eliminated by actual mechanical removal and by the proper application of open drainage and wet dressings

Protein Metabolism Protein is an absolute necessity for wound healing Hypoproteinemia retards fibroblastic proliferation Adequate protein reserves and a high protein diet accelerate fibroplasia The maximal tensile strength of a wound is reached in a shorter period of time in rats receiving high protein feedings than in those animals on a standard diet Ravdin found that 72 per cent of the wounds of hypoproteinemic animals either failed to heal or disrupted In a study of wound disruption in patients Hartzell, Wingfield and Irvin found either a protein deficiency or a vitamin C deficiency or both Furthermore, there is evidence which would make it appear that delayed wound healing is partially due to the reduction of the colloidal osmotic pressure of the plasma When nutritional edema was prevented in markedly hypoproteinemic dogs by giving adequate amounts of gum acacia, healing occurred and normal fibroplasia was observed

Resistance to infection in large part depends upon the body's immunologic responses, Antibodies are globulins present in plasma Protein deficiency thus decreases antibody production and reduces the intensity of the immunologic reaction

Many workers have studied nitrogen balance and loss in patients with large open wounds Particular attention has been focused on the burn ulcer Taylor, for example, found as much as 45 Gms of nitrogen excreted by one patient in a 24-hour period and directed attention to the inevitable result of the accumulative loss

Co Tui determined quantitatively the nitrogen loss in body exudates Slabs of fine pored celluloid sponges were used to collect the wound secretions In a 24-hour period one patient exuded 2 26 milligrams of nitrogen per square centimeter while another exuded 42 milligram of nitrogen per square centimeter from a denuded surface resulting from an avulsion The significance of the loss is emphasized by pointing out

beneath the skin the underlying tissues had failed to heal Histological studies showed a marked decrease in intercellular substance and lack of capillary formation Immediately after the biopsy Crandon received 1000 milligrams of vitamin C intramuscularly The second biopsy was obtained 10 days later At this time the wound showed good healing and there was ample intercellular substance Wounds fail to heal in patients with marked and long standing vitamin C deficiency More recently Wolfer studied the effect of prolonged ascorbic acid deficiency on young healthy males A diet with a low vitamin C content was maintained for seven months following which time incisions were made Subsequently the healing process was studied by removal of biopsy specimens at intervals of four to 14 days It was found that after 10 days the depleted subjects had developed only 30 per cent as much healing power as had the controls and that the fascia was about one half as strong The necessity for the administration of vitamin C both pre- and post operatively is clear 1000 milligrams given daily for several days should be enough to saturate even a grossly deficient patient. The Medical Division of the National Research Council recommended a daily oral intake of 75 milligrams in all wounded men in the service until recovery was complete

There have been many conflicting reports regarding the relationship of vitamin A and the B complex to wound healing The most con spicuous ill effects of vitamin A deficiency are changes in the epithelial tissue Epithelial atrophy and disquamation are followed by keratiniza tion In elderly patients with atrophic skin and many keratotic lesions, an increase in their vitamin A cannot help but be beneficial in healing of skin grafts and other cutaneous wounds

The vitamin B complex includes a large number of factors, some of which are little known The circulatory manifestations of B_1 deficiency should be particularly suspected in the indigent and low income groups of persons who have faulty diets and food idiosyncrasies.

Anemia Anemia is generally recognized as a complication of any extensive wound This anemia is frequently progressive and accom panied by marked debility At times it is so severe that there appears to be little impetus to wound healing prior to the administration of massive whole blood transfusions Profound anemia, *per se*, is con sidered by many not to retard wound healing, for severely anemic patients most often have protein and vitamin deficiencies which may account for the poor healing usually observed

The problem of anemia in the burn wound has been studied by Moore and others They suggest several factors which may participate

esses These substances play a far more fundamental role in the living organism than is evidenced by the prevention and cure of the classical syndromes of pellagra, beri-beri or scurvy Thiamin and nicotinic acid are essential to the enzyme systems regulating carbohydrate metabolism Riboflavin participates in both amino acid and carbohydrate utilization Vitamins are necessary for optimum wound healing They form an integral part of tissue repair

The basic physiological role of vitamin C is the assurance of normal production and the maintenance of intercellular connecting or cement substances of the supporting tissues of the body particularly collagen Deficiencies in ascorbic acid cause the body to produce faulty collagen Likewise the preformed collagen may undergo liquefaction and absorption In either case mechanical support of the tissues is markedly diminished

The hemorrhagic tendency in vitamin C deficiency as manifested by capillary fragility, is attributed to the weakening of the intercellular substance in the blood vessel walls Vitamin C deficiency furthermore impairs the production and maintenance of the intercellular substance related to the growth of fibroblasts

Comprehensive studies of ascorbic acid in relation to healing have been carried out by many workers in recent years Lauber and Rosenfelt used a cytological staining method to demonstrate significant quantities of vitamin C in young granulation tissue and in the surrounding skin Lanmin and Ingalls and Taffel and Harvey showed the tensile strength of healing wounds to be considerably less in animals with a partial ascorbic acid deficiency than it was in normal controls Histological study of these wounds showed the scar tissue to be definitely abnormal The fibroblasts were arranged in a disorderly manner and there was a very marked decrease of intercellular substance Bourne found a relationship between the total blood vitamin C and wound strength Jones and his colleagues, moreover, have proven that the tensile strength of an operative wound scar in guinea pigs is directly proportional to its vitamin C content,

Crandon showed rather dramatically the necessity of ascorbic acid for wound healing in the human patient This worker placed himself on a vitamin C free diet for a period of six months After three months had elapsed a wound was made in his right mid-back On the tenth postoperative day a biopsy of this wound showed good healing At the end of six months, when the plasma vitamin C had been zero for some time, a similar wound was made It appeared to be healed also On the tenth postoperative day a biopsy was taken It was found that

patients with extensive burn wounds Menses cease after severe burns and usually do not commence again until the open wound is completely healed Cope encountered an increased growth of hair in six female victims of the Cocoanut Grove fire In five of these the growth occurred chiefly on the cheeks, lips, chin, and neck In all six there was an increased amount of hair on the upper and lower extremities With the return of menses the hair began to disappear These manifestations were accompanied by an increased excretion of the 17 ketosteroids Lund, following the suggestion by Browne, has used testosterone proprionate with what he describes as considerable clinical success in the later stages of burns The pain decreased and the granulations improved This hormone had equally good effect upon the male and female patient Possibly the changes in sex hormone excretion is but another manifestation of altered adrenal cortical function, a complication recognized in the severely burned patient

General Debilitation Marked weight loss and general debilitation occur as serious complications in patients with large chronic ulcerating wounds This latter term serves simply to summarize the combined effects of infection, hypoproteinemia, pain, fever, anemia, inability to take and metabolize adequate amounts of food, and loss of morale through pain and disability General debilitation can be prevented only by attaining a healed state A concerted effort should always be made to obtain wound healing before this degree of debilitation develops

Topical Applications to Speed Wound Healing The complex nature of tissue repair makes it seem highly improbable that the topical application of any magic drug will hasten wound healing and eliminate scarring Through the decades many agents have been acclaimed Byars and Letterman have pointed out that "the wound characterized by part thickness loss of skin should heal without scarring or with minimal scarring unless further loss of tissue is produced through the use of topical applications, improper dressings, or infection With the full thickness loss of skin, especially over large areas healing must be by slower body processes Treatment which holds infection to a minimum supports the general condition of the patient, and does not injure tissue will result in the most rapid spontaneous healing possible No topical agent alone can achieve these ends"

TISSUE TRANSPLANTATION

Transplants Tissue transplantation is an ancient art Its establishment upon a scientific basis however has been achieved within the last century and the practical application of grafts and flaps is really a development of the past two decades In the medical history of World

in red cell loss early hemolysis and cell fragility, blood destruction by unneutralized plasma antibodies, blood loss through the open wound, infection, disordered iron metabolism, and depressed marrow function They found occasionally that multiple closely placed transfusions failed to restore the red cell volume, but there was no evidence to support the contention that such transfusions inhibit bone marrow "Undoubtedly the gradual replacement of losses as they occur is more economical of blood as well as more physiologic Delay in blood replacement is followed by substitution of extracellular fluid for the lost red cell mass, with restoration of total blood volume and a low peripheral red cell concentration Delayed replacement produces an expanded blood volume which results in an increased cardiovascular load and, possibly, compensatory destruction of a portion of the infused cells."

Blood Supply of the Part The vascularity of a part and the integrity of the blood supply to that region have long been known to constitute important factors in wound healing Any mechanical restriction of the arterial blood supply will interfere with healing although more retardation probably is due to the poor venous return Tight, constricting bandages, pressure from splints or pads, excessive suture tension, and stress from hemorrhage within the tissues are some of the more common mechanical causes of non-healing

In well vascularized areas, such as the face, wounds heal with much greater rapidity than in a region with a limited blood supply or where the blood supply is dependent and somewhat stagnant When the blood supply of an area has been damaged by vascular lesions, such as is observed in varicosities, the wounds show little or no tendency to heal

Blood Volume Diminished blood volume is a common accompaniment of persistent unhealed wounds This reduction in volume occurs simultaneously with an increase in the interstitial fluid Reductions of 1500 to 2000 cubic centimeters in blood volume were found in a study of soldiers with long standing open wounds Interstitial volumes of 4 to 7 liters above the standards of the patient's observed weight represent an even larger interstitial fluid mass when the standard weight prior to injury is considered The syndrome of "chronic shock" has been characterized by Clark as an increased "susceptibility to shock correctable by transfusion replacement of the blood volume deficit" The patient with an unhealed wound, a demonstrable weight loss, and a reduced blood volume is a victim of this syndrome This concept of chronic shock is useful in the routine management of the large ulcer It serves as a working tool in the face of apparently conflicting laboratory determinations and clinical studies.

Internal Secretions Hormone imbalance has been demonstrated in

of reestablishing the arterial and venous circulation, such as cutaneous epithelium, cornea bone, cartilage, and fascia, provide particularly successful grafts. Grossly these tissues live and grow The ultimate fate of the actual cells transplanted has given rise to several theories Some believe that the graft itself persists and becomes an integral part of the host Others feel that the transplanted cells are absorbed and that the stroma alone survives, serving as a network for the migration of regional cells into the area It is the opinion of still others that the entire trans plant is eventually replaced by local tissue

Heterogenous Transplants Heterogenous grafts are obtained from one organism and transplanted to another Isografts consist of tissue taken from one individual and transferred to another of the same species, while Zoografts are made up of tissues taken from animals of different species Isografts have never been demonstrated to persist indefinitely except in the case of identical twins Isografts composed of the more avascular tissues have proven, however, of inestimable valuable in reconstructive surgery The transplantation of tissues from animal to man has been impractical

Grafts and Flaps. The transplantation of skin and its underlying adipose tissue is one of the most extensively used procedures in plastic and reconstructive surgery A free skin graft is one in which the transplanted skin is completely removed from the donor site and transferred to a recipient area. A pedicle graft or flap retains a connection with the donor site although attached to a new location In some instances when the flap establishes vascular and tissue continuity with the recipient area, the pedicle is cut This method of transplantation was practiced in antiquity

Skin Grafts The Reverdin or pinch graft includes the whole epi dermis and a small amount of dermis with a surface area of 0.3 to 0.4 square centimeters or less. Deeper sections of the skin, however, give much better results Davis introduced and used rather extensively this thicker graft he coined the phrase "small, deep graft" to describe it Today there are few if any indications for employing pinch grafts or the small deep graft The cosmetic result is imperfect. A carelessly selected donor site can later interfere with the taking of much needed split or full thickness grafts. Whenever a large repair is needed, a donor site for pinch grafts should never be selected on a portion of the body from which split or full thickness grafts can be obtained The flat, broad surfaces must be entirely avoided

Ollier Thiersch grafts are cut in sheets of skin rather than in tiny pieces as taken by Reverdin's and Davis' methods They are classically

War I the only mention of free skin grafting is contained in one sentence concerning an oral graft In the interim between the two great wars, the increasing mechanization of industry and the evolution of transportation resulted in accidents which encouraged the development and use of tissue grafts and transplants Civilian gained knowledge was then immediately applied in the second World War Surgery of the future will inevitably concern itself with the transplantation of tissues Ultimately diseased and vital organs may be replaced by normal functioning structures This will depend to a very great extent upon the discovery of fundamental facts of organismal specificity

Biologic Considerations The genetic relationship of the host and donor is of prime importance in determining the success or failure of a graft The investigations of Loeb have in part elucidated the connection of organismal relationship with tissue transplants "All or about all tissues in a given individual within a certain species have, in common, certain chemical characteristics which may be designated as the individuality differential, and in a similar manner all the tissues of near relatives, of different strains, varieties, species, genera and classes of animals have, in common, chemical characteristics, which may be designated as syngenesis, strain, variety, species (hetero), generic and class differentials These differentials determine the reaction between host and donor " In general, the closer the kinship the more likely the survival of the tissue transplant Thus, transplantations of tissue from sibling to sibling remain viable longer than those from parent to child

Loeb's conclusion "that the organismal differentials are due to the genetic constitution of the organisms is based on the correspondence between the characteristics of the differentials and the relative intensity of the reaction against strange differentials on the one hand, and the genetic relationship of the organism which are the bearers of the differentials, on the other hand " The genetic compatibility between the donor and host apparently depends upon the sum total of genes composing the chromosomes The gene derivatives determine the differentials, the magnitude of reactions between host and donor is in direct proportion to the similarity of the genes The sex chromosome, however, appears to be of little significance Tissue transplants are defined on the basis of their genetic compatibility

Autogenous Transplants Autogenous grafts are obtained from and transplanted to the same individual The initial viability of an autogenous free graft depends upon the interchange of tissue fluids made possible by the firm cohesiveness of transplant to host Those tissues with low metabolic rates and for which there is no immediate need

many relentlessly destructive systemic effects into a temporarily well healed area Isografts are indicated (1) whenever a severely injured person does not have a sufficient amount of his own skin to cover the denuded portions of his body, (2) when the patient cannot be gotten into suitable general condition to undergo a major skin grafting procedure, and (3) when the patient is failing daily from debilitation and pain in spite of all supportive and therapeutic measures While these grafts are in place the turning point in the patient's recovery often occurs Epithelization is stimulated and biochemical and physiologic restoration is achieved

Full thickness skin grafts are not put over large raw surfaces because the size itself is prohibitive and the success of a full thickness graft is uncertain in contaminated fields There are two basic requirements for the use of such a graft. It should be applied to an aseptic field in which complete hemostasis has been obtained This graft is highly useful in the resurfacing of healed deformities where it is extremely desirable to have a minimum amount of skin shrinkage following operation Perhaps the most clear cut indication is in the repair of eyelids The texture and color of the post-auricular full thickness graft make it preferable for use on the face

Skin Flaps Heavier restorations than free skin grafts are not infrequently necessary, direct regional or delayed pedicle flaps are then used These flaps are most often required in facial reconstructions and for the repair of the extremities following deep losses They are indicated when secondary operations in the restored areas are contemplated they provide the only adequate covering for tendons and bone available The types and designs of regional transposed and rotational flaps are numerous The varieties of distant flaps provide material for reestablishing surface continuity at all points of the body When planning a flap it is essential that the patient's comfort be considered, a suitable donor site selected, the wound prepared for transfer, and the design for the flap carefully worked out The transfer of a flap should be accomplished in as few operations as possible

At the time of transfer, hemostasis is essential, and the edges of the flap must be carefully sutured to the surrounding skin, The donor area should be grafted and all raw surfaces eliminated Usually flaps may be divided about the fourteenth day Flaps from the opposite arm are preferred for covering the fingers, interdigital spaces, and the palm of the hand Abdominal flaps are best for the dorsum of the hand forearm and elbow Thorocobrachial flaps are useful in arm repairs For the lower extremity, crossleg flaps are more comfortable

composed of epidermis, but actually the superior portions of the papillae of the dermal layer are usually included, Since these grafts contain little derma they are really too thin to provide adequate and durable protection for areas subjected to repeated friction or sustained pressure Even under slight trauma the grafted surface is likely to break down resulting in a slow healing ulceration Thiersch grafts find their greatest usefulness in the replacement of appreciable losses of mucous membrane and in the covering of very extensive burn surfaces where the donor area is quite small. The donor site heals very rapidly and with little scarring, thereby allowing many successive crops of skin to be obtained in fairly rapid order from the limited field.

The thick split-skin graft of Blair and Brown incorporates one-half to three-fourths of the full thickness of the skin, It is undoubtedly the most widely used method of repairing denuded skin areas The greater thickness of the graft makes it more durable and resistant to injury and results in a more normal appearance It has few of the shortcomings of the thin Ollier-Thiersch graft and many of the attributes of the full thickness skin graft.

Various devices have been used for cutting and applying split grafts The Blair knife with its Ferris Smith modification is perhaps the simplest It consists essentially of a long knife of the amputation variety with a very sharp detachable blade Padgett's ingenious dermatome and the numerous refinements of this basic principle made the widespread use of split grafts possible The new electric dermatome enables even the novice to remove split grafts accurately

Large sheets of skin can be obtained by the foregoing methods without cutting into the subcutaneous tissue, the donor site then rapidly heals The skin glands and appendages that remain in the deeper layers of the derma undergo a metaplasia into squamous epithelium which covers the surface in from eight to ten days The donor sites are dressed carefully with rayon, nylon, or fine mesh grease gauze, the dressing is allowed to remain in place from ten to fourteen days As high as five successive crops of skin have been obtained from one area over a period of six months.

It is possible to use successfully autografts that have been stored for several days, but this fact is not very important clinically, especially with regard to split grafts, for the latter can be cut rapidly and add but little time to the operation

Isografts consist of sheets of skin of split thickness depth taken from one individual and transplanted on another Although such skin does not persist, it can quickly convert an extensive open wound with its

are of particular value in restoring facial contour Fat grafts have been used to obliterate dead spaces and replace brain losses, they have aided in collapsing the lung, and in preventing adhesions about tendons

Fascia Fascia is one of the most widely used tissue transplants It has a low metabolic rate and is able to obtain its nutrition by osmosis prior to reestablishment of circulation in the recipient area The material maintains its identity It is resistant to infection, strong, and durable Grafts are most frequently obtained from the deep fascia of the thigh and abdominal wall Fascia is employed in the repair of hernias, for the correction of facial paralysis, and reconstruction of tendons Immediately after implantation into the recipient area there is a mild inflammatory reaction about the graft As soon as new vessels are established the reaction subsides and the fascia takes on its original histological structure and maintains its tensile strength

Nerve Grafts Nerve grafts are indicated whenever there is a loss of continuity in a peripheral nerve trunk which is so extensive as to make an end to end approximation impossible under any circumstances The majority of workers in this field feel that the autogenous type of graft provides the best possibility of success However, suitable material is often impossible to obtain from the same individual without the sacrifice of other useful fuctions The anterior femoral cutaneous nerve has proven satisfactory in bridging small nerve gaps it has been employed by Duel and Ballance in their work on facial paralysis

On occasion an amputation and nerve graft are indicated in the same patient. This provides a choice of material for grafting Isografts are readily available and, therefore most applicable in the majority of cases Both fresh and degenerated segments of nerves have been transplanted Duel reported three successful isograft transplants in six cases of facial nerve graft Davis believes that fresh isografts should be used to repair large defects The distal suture line is then resected and resutured as a later secondary procedure, thus, the axons growing down within the graft can penetrate into the distal segment through a less dense suture line Seddon and Holmes examined the remains of three isografts after they had been imbedded for 371, 425, and 573 days respectively Fresh grafts were used in two cases Upon examination of these practically nothing remained of the original nerve elements only long chords of fibrous tissue were found In a graft stored for 14 days in Ringer s solution the transplant was completely dead and was undergoing phagocytosis It was concluded that, in spite of the encouraging results with nerve isografting in small animals, in the human the implanted tissue provokes a cellular reaction of such mag

than the closed carried flap Nevertheless, defects of the leg too extensive to be covered by a crossleg may be rapidly repaired by an arm carried flap Improper postoperative care, infection, and necrosis may lead to flap failure

Mucous Membrane Grafts. Mucous membrane transplants are most useful in reconstruction of the inner aspects of the eyelids when a functional globe is present They are the lining of choice for the anophthalmic orbit The grafts are taken from the buccal mucosa, nasal turbinates, and vagina The technique of obtaining the tissue and its implantation on the recipient area is similar to that used in skin grafting. The procedure is never completely aseptic because of the nature of the donor site Mucous membrane grafts have the same growth characteristics as skin grafts They have the special attributes of being free of hair and desquamation.

Corneal Grafts: There are in general three types of corneal transplants The use of full thickness whole corneal grafts has been abandoned, opacities develop in almost 100 per cent of the cases Lamellar grafts are composed of a circumscribed area of superficial cornea, they replace a like amount of excised opaque tissue By this method, Fuchs was able to obtain improvement in only two out of 30 cases The most universally successful method of corneal transplantation consists of a free full thickness corneal graft four to five millimeters in diameter Such a graft may be obtained from the patient's opposite eye if it happens to be blind and the cornea usable, it may be taken from the non-opaque periphery of the cornea of the same eye, or isografts may be employed Material for this latter type of transplant is obtained from the cornea of eyes enucleated as a result of trauma, from fresh autopsy specimens, and stillborn infants In selected cases results are dramatic Their applicability, however, is limited They are useful only in replacing corneal opacities of otherwise normal eyes These opacities most often are the result of healed ulcers, interstitial keratitis, and burns

Dermofat and Fat Transplants Free fat transplants retain their identity, the original fat continues to live and grow Nevertheless, a rather marked absorption of the graft occurs, the bulk is reduced 50-75 per cent over a period of four to six months The uncertainty of the degree of shrinkage has led largely to the use of such transplants in combination with derma A dermofat transplant is obtained by removing a split thickness skin graft from the donor site prior to removing en bloc tissue composed of derma and fat The split graft is then resutured over this area to close the donor site Dermofat transplants

Blood Vessel Grafts The introduction of the anti-coagulants has opened a wide field in vascular surgery, the clinical value of blood vessel transplantation has become definitely established Arteries and veins have been grafted into the same person and into other individuals with apparent success The viability of the vessel when implanted, the genetic relationship of donor and recipient, and the technique applied, are of special importance in determining the fate of the transplant The applications and possibilities of this type of graft are dealt with fully in the discussion of blood vessel surgery

Cartilage Transplants In plastic surgery it is often necessary to reconstruct features and restore contours that have been lost or were congenitally absent Soft tissue restoration has to be made with the patient's own tissue The support such as is required for a nose, ear, or orbital border can be supplied by cartilage obtained from the individual or by that obtained from some other person Hyalin cartilage has the widest variety of uses It is available in large quantities from the costal cartilages Elastic and fibrous cartilage, however, have also been successfully implanted

Preserved isografts and fresh autocartilage have their individual merits Cartilage is lymph nourished, maintains its identity, and is not readily absorbed Isografts initiate a mild inflammatory reaction on the part of the host Nevertheless, they are ultimately tolerated indefinitely as foreign bodies Gradually fibroblasts grow into the graft and occasional areas of calcification appear These changes do not, however, alter the original design

Bone Bone grafts are used for healing ununited fractures, bridging bony defects where rigid support is required, and restoring skeletal contour The crest of the ilium, the anterior surface of the tibia and, to a much lesser extent the fibula or a rib provide convenient sources from which the transplant may be obtained

The success of a bone graft, like any other graft, depends upon the rapid reestablishment of its interrupted blood supply Any scar tissue surrounding the graft any hematoma separating the graft from the neighboring tissue or any infection is likely to lead to a poor result.

The viability of bone grafts immediately after transplantation is undecided The prevalent opinion has been that most of the bone dies but becomes revivified and regenerated by the ingrowth of *osteoblasts* accompanying the invading vessels This process undoubtedly occurs in dead bone transplants

The introduction of the use of radioactive isotopes as tracer elements has provided another approach to the problem of viability On the basis of comparative ratios of assimilated radioactive phosphorous, it seems

nitude that the graft is entirely replaced by fibrous tissue Eden also showed that the axons in an isograft undergo necrosis and are gradually replaced by fibrous tissue It has not, however, been proved that this is invariably the case in man Cablegrafts consisting of many strands of small nerves bridging a single defect in a large nerve trunk are apparently doomed to failure because of the scar tissue formation which develops about each of the trunks constituting the cable

Muscle Grafts and Flaps Free muscle transplants are rarely used for reconstructive purposes as they gradually undergo degeneration and are replaced by fibrous tissue Small fragments of muscle tissue have proved, however, particularly valuable in control of hemorrhage during neurosurgical procedures Muscle flaps in which both the nerve and blood supply remain intact are valuable in the correction of ptosis and have been advocated for the repair of facial paralysis In free nipple grafts made during the course of mammoplasty procedures there is in some cases preservation of the contractility of the nipple which is attributed to smooth muscular tissue transplantation

Tendon Grafts· Tendon grafts serve to reestablish the continuity of a tendon following segmental loss of this structure when the gap is too great to be closed by direct approximation of the two remaining segments Tendon grafts replace damaged, scarred, and immobilized segments and are very frequently needed in secondary tendon repairs These transplants take well and are mechanically efficient when a gliding mechanism is provided Epitendon is always transplanted with a graft and peritendon fat is used to provide the gliding surface Newly imbedded tendon is first nourished by the surrounding lymph and interstitial fluid Soon it becomes vascularized The deep central portion of a transplant shows spotty necrosis at the end of the first week These areas are very quickly replaced by growing tendon cells towards the end of the second week The more superficial part of the graft lives as such An aseptic inflammatory reaction surrounds the graft for the first two to three weeks but after this time rather quickly subsides By the end of four or five weeks the grafted tendon is as strong as a sutured tendon of the same age The success of a tendon graft is roughly indirectly proportional to its circumference Larger tendons are of such diameter that a considerable portion of their center undergoes necrosis A thick single strand of fascia lata is preferable for bridging the gaps of large tendons When tendon isografts are used the graft fails to live as such but is slowly replaced by living tendon tissue The results, however, have never been as satisfactory in Bunnel's experience The graft is yellowish in color, more adherent to surrounding structures, and occasions a greater inflammatory response on the part of the host

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reasonable to reach the tentative conclusion that transplanted living cancellous bone continues to exist as a vital graft with its own blood supply It integrates itself almost at once as a vital part of the system Devitalized boiled bone shows only a 7 per cent uptake of phosphorous, probably due to absorption, as compared to normal bone, live transplanted iliac bone assimilates 60 per cent of the normal in the first 24 hours and rapidly approaches 100 per cent within the next four days Refrigeration diminishes the immediate uptake but does not decrease the ultimate recovery beyond the initial period On the basis of clinical observations and this and other experimental evidence, it is felt that the best results can be obtained by using viable autogenous cancellous bone grafts

Gland and Organ Transplants. The transplantation of glandular tissue and entire organs is still in an experimental stage Autogenous kidney transplants were shown by Deederer to function satisfactorily Williamson has reported that an autogenous kidney implanted in the neck maintained the renal health of an otherwise normal animal The renal artery was anastomosed with the carotid, and the renal vein with the internal jugular The ureter was brought out to the surface of the neck Homologous kidney transplants, however, made in exactly the same manner have survived for only a short time One of Deederer's isografts functioned for 18 days

Ultimately it is to be hoped that diseased and vital organs may be replaced by normally functioning homologous transplants Technically such procedures are feasible and have been accomplished The organismal specificity of tissues and organs remains unsolved

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Chapter VI

MECHANICS OF RESPIRATION

UNDER normal conditions the pleural cavities are potential spaces filled completely by the lungs except for a small amount of serous fluid that serves as a lubricant between the visceral and parietal pleura during the act of respiration The large amount of elastic tissue within the lungs causes the organs to attempt constantly to pull away from the chest wall This elastic retraction is counteracted by the strong adhesive force between the two pleural surfaces The mechanical situation results in the creation of a negative pressure within the pleural space, which is considerably less than that of atmospheric air

During the act of inspiration the chest wall is pulled away from the lungs, the counterforce of the lungs becomes greater and the intrapleural pressure more negative Reduction in intrapleural pressure is greatest during inspiration and at the end of deep inspiration the pleural pressure reaches its maximum negativity During the act of expiration, intrapleural pressures are raised or less negative Even during the act of expiration, however, the pressures do not equal atmospheric pressure This is in counter-distinction to intratracheal pressures, which do actually exceed atmospheric pressure during expiration

INTRAPLEURAL PRESSURES

There is considerable variation in normal intrapleural pressures in different individuals A reasonable average, as expressed by Donders, places the values of minus 9 millimeters of mercury at the end of inspiration and approximately minus 7 5 millimeters of mercury at the end of expiration

The balance of negative pressure within the thorax is essential to life and if materially altered will result in extreme respiratory embarrassment and eventually death The mechanics of respiration may be simplified for purpose of description by considering inspiration as merely enlargement of the thorax, increasing the negativity of intrathoracic pressures and therefore causing the air to enter the lungs The reverse of this mechanism results in expiration

This conception of the mechanics of respiration would be deceptive, however, if accepted completely Morphologically, the lungs are com

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clinical importance when there is interference with the exchange of gases in the lungs With stretching and subsequent loss of elastic tissue, oxygen saturation of arterial blood will become diminished even during rest and on exertion may be dangerously impaired As residual air increases, the passage of CO_2 from the lungs and consequent marked increase of CO_2 tension will be found in both arterial and venous bloods The volume of breathing will become increased under these circumstances in an effort to compensate for the increase in CO_2 and decreased arterial oxygen saturation

Residual Air Determination There are two methods to measure residual air in the human subject A technic popularized by Cournand and Darling depends upon the measurement of the rate of nitrogen excretion in a subject inhaling 100 per cent oxygen Patients with increased residual air resulting from emphysema or other causes will have impaired diffusion of gases and excrete larger concentrations of nitrogen for a longer time than normal subjects

McMichael has employed a modification of the Christie method to measure residual air This is accomplished by using an inert gas, usually helium or hydrogen, in a closed circuit spirometer from which CO_2 is absorbed by soda lime Oxygen is added at a rate equal to the oxygen consumption of the patient The subject breathes into the spirometer which contains a known percentage of inert gas (helium or hydrogen) mixed with air A katharometer measures the percentage of inert gas After a few minutes the inert gas will diffuse into the respiratory system making the percentage of the inert gas in the spirometer equal to the percentage of inert gas in the respiratory system

The volume of space contributed by the subject can then be calculated The initial volume in the spirometer substracted from the final volume will give an amount equal to residual air and supplemental air of the patient The value of supplemental air is known from standard spirometer measurements Residual air volume is then established

Tidal Air Tidal air is the amount of air taken in during ordinary respiration In the average sized adult this amounts to about 500 to 600 cubic centimeters

Complemental Air At the end of ordinary inspiration, the vigorous forceful effort to take in more air will usually result in intake of from 1500 to 2000 cubic centimeters This is known as complemental air

Supplemental Air A forced expiration usually results in the exhalation of about 1500 cubic centimeters, known as the supplemental air

Vital Capacity Tidal air plus complemental air, plus supplemental air gives the value of the vital capacity, which in the simplest terms

posed of a complex system of lobes, bronchopulmonary segments and lobules Functionally these organs respond to a highly integrated neuromuscular system

A large number of muscles are involved in each respiratory act The thorax is enlarged by elevation of the ribs which respond to the actions of the external intercostals and serratus posticus superior, and there are, in addition, the accessory muscles of respiration which include the scaleni, the trapezius, the rhomboids, sternocleidomastoids, serratus anticus and others Enlargement of the thorax from above downward is accomplished chiefly by the diaphragm The right dome of this organ will descend as much as 12½ to 13 millimeters and the left dome about 12 millimeters Protrusion of the abdominal wall resulting from the descent of the diaphragm causes some displacement of the abdominal viscera

The internal intercostal muscles are considered by some as the most important muscles of expiration since their action will pull the ribs together Muscle action in the act of expiration, however, is not as important as during inspiration When the inspiratory muscles cease to act the thorax tends to diminish in size and the elastic tissue of the lungs acts to empty them of air In addition, in this phase of expiration there is a shortening and narrowing of the bronchi resulting from action of intrinsic muscles in the wall of the bronchi The abdominal muscles also have expiratory functions During normal quiet breathing their action is slight, but in vigorous or forced breathing they may contract strongly and push the diaphragm upward

Effects of Intrapleural Pressures on Circulation The negative intrathoracic pressure which results in normal respiration has other important physiologic functions The passage of blood into the large venous trunks and probably into the auricles of the heart depends largely upon the sucking action of the negative pressure These same factors are of importance in maintaining normal lymph flow throughout the body

PULMONARY VENTILATION

Residual Air. Once the lungs become inflated at the time of birth, it is impossible to exhale all of the air contained in them The amount of air remaining in the lungs at the end of a maximal forced expiration is known as *residual air* The residual air normally amounts to about 1500 cubic centimeters in the average adult

Certain diseases, principally emphysema and asthma, may be accompanied by increases in the amount of residual air and become of

clinical importance when there is interference with the exchange of gases in the lungs With stretching and subsequent loss of elastic tissue, oxygen saturation of arterial blood will become diminished even during rest and on exertion may be dangerously impaired As residual air increases, the passage of CO_2 from the lungs and consequent marked increase of CO_2 tension will be found in both arterial and venous bloods The volume of breathing will become increased under these circumstances in an effort to compensate for the increase in CO_2 and decreased arterial oxygen saturation

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Vital Capacity Tidal air plus complemental air, plus supplemental air gives the value of the vital capacity, which in the simplest terms

may be defined as the greatest amount of air which can be exhaled after the deepest possible inspiration Normal vital capacity is in the neighborhood of 3500 cubic centimeters in the average sized adult It varies considerably with age, build and sex and is usually slightly lower in females than males Vital capacity determinations furnish a rough index of the respiratory reserve of the individual

Alveolar Air: The alveoli of the lungs will contain about 3000 cubic centimeters of air at the end of ordinary expiration The amount of air taken into or removed from the alveoli at any one time is small and this volume of air retained in the lungs prevents sudden changes in temperature and chemical composition of the gases, maintaining, under normal circumstances, a smooth, even character of respiratory movements

Dead Space Air The so-called dead space of the respiratory tree amounts to about 150 cubic centimeters of air, which is found in the trachea, pharynx and broncial tubes This volume is constant in both rapid and slow breathing, but will effect pulmonary ventilation when the respirations are shallow Respiration is more effectively improved, therefore, by greater depth of breathing than by a faster rate It is important to remember that during inspiration, if the tidal air taken in is 500 cubic centimeters, only 350 cubic centimeters are of physiologic importance, since the amount of dead space air must be deducted from the total

Bronchospirography Bronchospirography was first accomplished by Jacobaeus and his associates Many technical improvements have been presented during the past few years as various types of bronchospirometers have been perfected

With this method it is possible to establish to what extent each lung contributes to total pulmonary function Of particular interest is the ability to study the extent of compensatory changes that may result from damage to part or all of one lung

Separate samples of gas are obtained from each lung Both single and double lumen catheters have been employed for this purpose The samples are collected in spirometers Oxygen consumption, CO_2 excretion and ventilation of each lung can be determined accurately by the method The most important determinations for clinical purposes are relative O_2 consumption, vital capacity and minute ventilation For details of technic and a description of the various types of bronchospirometers, the reader is referred to the excellent works of Jacobaeus, Cournand and his associates, Pinner, Leiner, Wright, Harod, Gebauer and Adams

Spirography The performance of bronchospirography requires considerable experience and the knowledge of rather complicated technics Valuable graphic registrations of breathing can be obtained, however, by spirography employing only a modified basal metabolism apparatus Cournand and his associates in their important contribution to this subject have emphasized the value and simplicity of the method They have shown that the essential features of pulmonary function are 1 Air circulation, e g, movement of air between the atmosphere and the pulmonary alveoli 2, Diffusion of gases between alveoli and pulmonary capillaries 3 Adequate circulation of blood through the pulmonary vascular bed

The following spirographic tracings, recommended by Cournand, will furnish significant and sometimes quantitative information 1 Quiet breathing 2 Deep breathing (vital capacity) 3 Maximum deep breathing capacity 4 Maximum breathing capacity

Quiet Breathing This tracing will show the depth and rate of quiet breathing Retardation of either inspiratory or expiratory phases, irregular breathing and other variations may be demonstrated

Deep Breathing (Vital Capacity) A tracing is made to demonstrate vital capacity, e g, the greatest amount of air exhaled after deepest possible inspiration Just before the vital capacity is determined, complementary air is recorded by having the subject, at the end of normal expiration, take the deepest possible inspiration

Maximum Deep Breathing Capacity Reserve air is measured by recording the amount of air which can be forced out after normal expiration is completed This is followed by maximum inspirations and a succession of deep respirations The deep breathing capacity tracing will establish the vital capacity and its components.

Maximum Breathing Capacity A tracing is made with the subject breathing as rapidly and deeply as possible for 15 to 30 seconds

The result in maximum breathing are fairly constant whether speed or depth of respiration is stressed These tracings will usually be more significant than the ordinary vital capacity determinations Not only is the amplitude of breathing established but the dimension of time in relation to total pulmonary ventilation is provided

SOME PHYSIOLOGICAL CONSIDERATIONS CONCERNING THE LUNGS IMPORTANT TO THE SURGEON

Increase in Intrapleural Pressure The modification of intrapleural pressures in either direction, that is, reduction or increase in negativity, is important to the surgeon An increase in intrapleural pressure is a

constant accompaniment of incision through the nonadherent pleura and also encountered when air is introduced into the pleura Paralysis of the muscles of inspiration or alterations in the bony framework of the thorax by removal of ribs will also raise the intrapleural pressure Depression of the chest by external pressure with tight dressings or bands acts in a similar manner and may embarrass respiration

Pneumothorax · Since the lung is subjected to considerable elastic tension its retraction follows any reduction in negativity of the intrapleural pressures Collapse of the lung may, therefore, be accomplished by a compressing force of less than atmospheric pressure The concept of pulmonary collapse by relaxation is fundamental and is applied in artificial pneumothorax therapy for tuberculosis and by a variety of surgical procedures

It is important to emphasize that the experimental studies of Graham and Bell have demonstrated that the production of unilateral pneumothorax may produce an elevation of pressure in the contralateral pleural space and effects not only the lung on the side in which the pneumothorax was induced but the contralateral organ

The normal, human mediastinum is mobile within certain limits and consequently the induction of pneumothorax on either side will result in a rise in intrapleural pressure on both sides If the mediastinum is thickened and fixed by inflammatory reactions, these effects are less marked

Elevation of intrathoracic pressure will diminish pulmonary volume and in turn decrease vital capacity This alteration in vital capacity must be considered when surgical operations upon the chest are contemplated Distressing dyspnea usually becomes evident when vital capacity is reduced to a figure less than three times that of the individual tidal air requirements, e g, approximately 1500 cubic centimeters, and life cannot be maintained when the maximal inspiratory efforts fail to provide the necessary volume of tidal air (Figure 14)

The degree of fixation of the mediastinum and the individual's vital capacity prior to alteration of pressure will determine his ability to withstand the pressure changes

Pendulum Air The mechanism of rebreathing, postulated by Brauer and termed "pendelluft" has been offered as an explanation for anoxemia produced by open pneumothorax This concept is based on the hypothesis that there is transfer of air from one lung to the other During the expiratory phase air from the lung on the sound side may enter the lung which is partially collapsed and the gases being re-aspirated into the more actively functioning lung during inspiration



FIG 14 Roentgenogram of chest demonstrating a tension pneumothorax.

Such paradoxical respiration would undoubtedly lower the alveolar oxygen tension and increase carbon dioxide concentrations There is some difference of opinion as to the relative importance of the pendulum like respiration as compared to the pure effects of altered intrapleural pressures and pulmonary collapse

Open Thoracotomy Operations upon the thoracic viscera necessitate a large incision into the chest The dangers of open thoracotomy depend primarily upon altered intrathoracic pressures and concomitant physiologic disturbances There is tremendous individual variation in the ability to tolerate induced diminution of vital capacity, pendulum respiration and the circulatory changes

Pressure Cabinets Early attempts to minimize the effects of the elevation of intrapleural pressure during operation included construc

tion of chambers to the design of the body of the patient and by partial exhaustion of the air from this chamber it was possible to maintain a degree of negative pressure in the exposed, open thoracic cavity Positive pressure compartments were also sometimes employed to enclose the head of the patient in order to raise the intrabronchial pressures and further obviate the tendency toward collapse of the lung These apparati were cumbersome and presented technical difficulties and expenses which made them impractical

Intratracheal Anesthesia The introduction of the technic of intratracheal anesthesia by Meltzer and Auer in 1909, made it feasible to deliver the anesthetic agent through the endotracheal catheter and at the same time maintain pressures greater than atmospheric, assuring inflation of the lung by augmenting the intrabronchial pressure to a level above that existing in the pleural space The less effective, but valuable technic, also was employed by exerting pressure through a tight fitting face mask This method, however, lacked certain advantages of endotracheal administration of the gas, namely, maintenance of a clear airway and lack of a route for direct aspiration of accumulated secretions in the trachea or bronchial tree Pulmonary ventilation is, of course, somewhat impeded since the act of expiration against pressure is altered The perfection of certain machines to maintain rhythmic insufflation of the lungs has also helped solve the problem of pulmonary ventilation while the chest is open

Postoperative Readjustments. After the performance of an open thoracotomy, the chest wall is closed as nearly airtight as possible Usually before the closure of the pleura the anesthetist raises the pressure in the lungs to produce almost complete reinflation of the organ The negative intrathoracic pressure, therefore, is established at the completion of the operation After major intrathoracic procedures there is the inevitable accumulation of serosanguineous exudates from trauma to the pleura Large accumulations will elevate the intrapleural pressure and produce dyspnea It is necessary, therefore, to provide drainage of these effusions either by aspiration with a needle or by catheter drainage, using a water-seal system Open thoracostomy drainage would, of course, merely continue the open pneumothorax and present an added hazard

The syphon action of a water-seal drainage system contributes sufficient suction to maintain a negative intrapleural pressure The degree of negative pressure developed depends in part upon the vertical distance between the level of intrathoracic tip of the catheter and the fluid level in the drainage bottle Stronger negative pressures may be



FIG 15 The appearance of atelectasis of the left lower lobe on roentgen examination.

obtained by the use of suction machines, but are rarely necessary

Aspiration of the Tracheobronchial Tree Accumulations of blood or mucus in the trachea or bronchi following intrathoracic operations may interfere seriously with respiration The airway must be cleared of secretions or partial suffocation and anoxia will follow Moreover, incomplete ventilation will interfere with early and adequate pulmonary expansion

Vigorous coughing will often remove bronchial secretions, but if respiratory exchange remains impaired, tracheobronchial aspiration is essential Suction through a soft rubber catheter inserted into the trachea will provoke coughing and sometimes relieve the obstruction

Visualization of the trachea and bronchi through the bronchoscope, with aspiration under direct vision, is more satisfactory therapy

Atelectasis. Partial or complete collapse of the lung, pulmonary lobes or segments may result from blocking of the lumen of the bronchi with secretions or foreign bodies Atelectasis is not uncommon following all types of operations and is a particularly important complication after operations or injuries of the chest Prompt relief is usually obtained by proper aspiration of the tracheobronchial tree (Figure 15)

Wounds of the Thorax. Open wounds of the thorax will produce pneumothorax unless there is a firm symphysis between the visceral and the parietal pleuras There is a high mortality rate associated with this type of injury, but open pneumothorax is not necessarily fatal Theoretically, the smaller the opening the better respiration can be maintained This factor is altered, however, by the individual's vital capacity which will determine roughly the size of pleural openings he may suffer and survive The aged and decrepit will die in most instances from an open wound of the chest Conversely, the rugged young man with elastic lung tissue and a high vital capacity may survive wounds of amazing proportions

Therapy must be directed to transforming the open to a closed pneumothorax and minimizing alteration of intrathoracic pressures Closure of an open, sucking wound producing a closed pneumothorax decreases mediastinal mobility and pendulum respiration As the intrapleural pressure is reduced the vital capacity will immediately increase Recurrence of dyspnea in cases of chest wounds usually indicates that either blood or air has accumulated in the pleural cavity

Penetration of the chest by small missiles or in closed wounds by the jagged edge of fractured ribs may result in the formation of hemothorax or pneumothorax in the absence of a sucking wound If the closed pneumothorax is of valvular or tension variety, increasing respiratory and circulatory distress will be prompt The treatment consists in aspiration of blood or air to adjust intrapleural pressures to the level compatible with satisfactory respiratory ventilation

It is important to remember that nonpenetrating injuries of the chest may produce significant alterations of intrathoracic pressures by the mechanisms just described Crushing, nonpenetrating wounds may also produce subcutaneous or mediastinal emphysema if the lung is torn and the pleural surfaces are fused The air will take the line of least resistance entering the soft tissues of the chest wall and may migrate over the entire body, particularly in the neck and the soft tissues of the face A more serious type of emphysema may result from the rupture

of a bronchus with interstitial transportation of the air along the sheaths of the pulmonary vessels and bronchi, resulting in the production of mediastinal emphysema, which if severe, may produce the syndrome of cardiac tamponade characterized by fall of systolic blood pressure, rise in venous pressure, muffling of heart sounds and eventually death if the pressure is not relieved Spontaneous recovery is the rule when only alveoli have been injured and the air is leaking into the chest wall A tear of the major bronchus furnishes a much more serious problem.

Decrease in Intrapleural Pressures Constriction or obstructions of the trachea or bronchi will cause a fall in intrapleural pressures Increases in the negativity of pressure have been observed experimentally and clinically during attacks of bronchial asthma, in atelectasis of either a lobe or a lung, and sometimes after the administration of bronchoconstrictor drugs The effect on the pressures is chiefly the result of reduction in the caliber of the respiratory passages, which are followed by important physiologic changes directly attributable to the alteration in pressure Displacement of the mediastinum and its contents, which accompanies the heightened negativity in unilateral atelectasis may result in the kinking of the great vessels and a resultant strain on the heart, which if carried to extreme will be accompanied by the development of cardiac decompensation. The greater negativity of intrapleural pressures during asthmatic attacks may constitute an important factor in alveolar dilatation and rupture This mechanism is probably the result of obstruction to the escape of alveolar air during the expiratory phase Lobar or lobular collapse of lung tissue may play an important role in the pathogenesis of bronchiectasis, since the elastic hypertension associated with decreased intrapleural pressures may produce distortion of the bronchi

Pulmonary Hemorrhage The blood pressure in the pulmonary circulation is low compared to the systemic vessels ranging from 20 to 30 millimeters of mercury The low pressures and the elastic quality of lung tissue which causes the organ to contract will sometimes prevent fatal hemorrhage from wounds of the lung Lack of high systemic pressures in the pulmonary vessels also accounts for the relatively low incidence of fatal hemoptysis

Major injuries to either the pulmonary arteries or veins may however, result in death Pulmonary artery bleeding is characterized by a flow of venous blood which pulsates feebly Hemorrhage from the pulmonary veins flows in a steady terrifying stream of bright blood If major tributaries of the pulmonary vein are injured in an open chest

Visualization of the trachea and bronchi through the bronchoscope, with aspiration under direct vision, is more satisfactory therapy

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the control of the hemothorax In this connection, it is important to emphasize that early reexpansion of the lung to conserve cardiopulmonary function is of prime importance Once active bleeding from the lung has stopped, there is practically no danger of producing secondary hemorrhage by gradual evacuation of blood from the pleura by aspiration (Figure 16)

The production of pneumothorax by air replacement after aspiration of blood is undesirable since lung expansion will be delayed

Chronic Hemothorax If blood is not removed from the pleura a clot will form and since blood is irritating to the pleura even in the absence of infection, the lung will become encased by a layer of fibrous tissue If this occurs, reexpansion of the lung can only be obtained by pulmonary decortication, which involves the removal of fluid and clot from the pleura and the surgical excision of the corset of scar tissue encasing the lung

Spontaneous Pneumothorax Spontaneous closed pneumothorax may result from escape of air into the pleura following injury of disease, which will rupture the surface of the lungs Perforation of the esophagus may produce pneumothorax and rarely, injuries to the abdominal viscus will cause gas to enter the pleura Tuberculous lesions of the lung are a common cause for the production of spontaneous pneumothorax

Probably the most frequent mechanism in the production of spontaneous pneumothorax is the rupture of an emphysematous bleb or blebs on the surface of the lungs This may occur in patients with severe emphysema and asthma, but is also common in people who are otherwise vigorous and healthy Recurrent attacks mav effect the same side or both sides Bilateral spontaneous pneumothorax is rare, but can occur Emergency treatment is the same as outlined for traumatic pneumothorax

Chronic Recurrent Pneumothorax Repeated bouts of spontaneous pneumothorax from the rupture of emphysematous blebs may require surgical intervention Extirpation of the blebs may stop the attacks If, however, there are many lesions it may be impossible to excise all of them Under these circumstances poudrage of the pleura should be performed Sterile talc and other irritating substances have been utilized to powder the pleural surfaces The purpose of the operation is to produce sterile pleurisy and cause firm symphysis of the pleural surfaces If this is accomplished obliteration of the pleural space will preclude further attacks of pneumothorax

Bronchopleural Fistula Bronchopleural fistula may result from

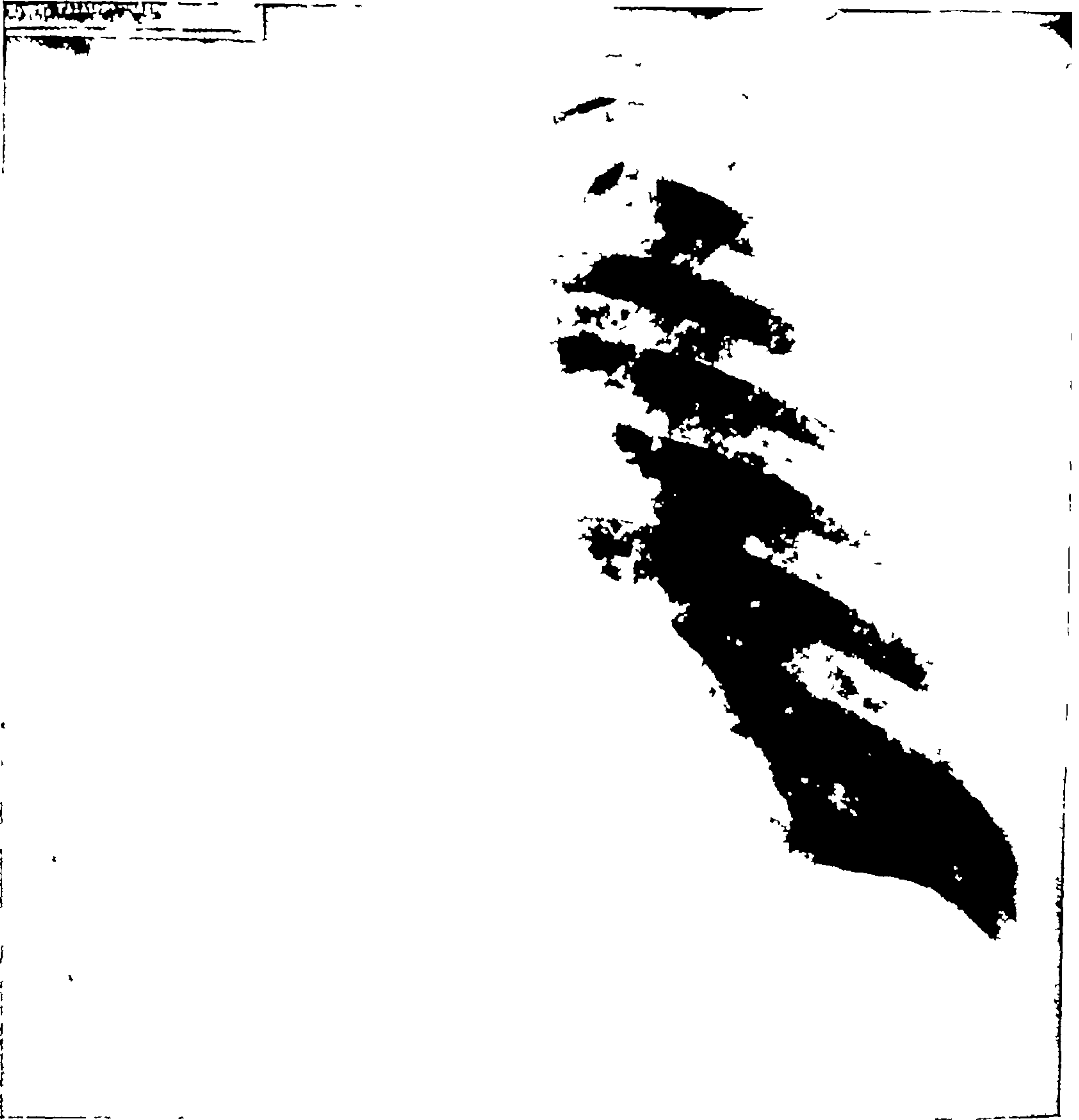


FIG 16 Roentgenogram of chest showing extensive hemothorax

wound, there is considerable danger of fatal air emboli Air may be sucked into the vessels entering the left heart and from there be pumped into the coronary and cerebral arteries

Pleural Shock Probably most cases of "pleural shock" are the result of air emboli resulting from injury to the pulmonary vein system, rather than a violent nervous reflex Death from air embolism, during or following thoracentesis, may result from this mechanism, or from air reaching the brain through the anastomosis of the intercostal, spinal and cerebral vessels This route has been demonstrated by the excellent anatomic studies of Batson

Hemothorax Hemorrhage from wounds of the lungs if not immediately fatal, usually subsides and the urgent immediate problem is

lung, for cancer and other lesions, is now a common procedure Bilateral operations for bronchiectasis have necessitated even more radical sacrifice of pulmonary tissue Graham and others have reported the successful removal of both lower lobes, the right middle lobe and the lingula of the left upper lobe (left middle lobe) for bronchiectasis It would be a mistake, however, to consider each lung, lobe or segment an independent physiological unit Functionally, the various anatomical components of the lungs perform as an integrated organ The important work of Van Allen and Lindskog has demonstrated collateral air drifts between the various pulmonary structural units There are also collaterals of the pulmonary circulatory system capable of carrying on enough exchange of blood between segments, lobes and lobules

Churchill has considered the conservation of the space occupying role of the lung as one of the most important functions of the air and vascular collaterals

Pulmonary Edema Edema of any part of the body is only a symptom of a variety of primary diseases Pulmonary edema is an important and formidable threat in patients of advanced age, who require surgical therapy

Cardiac edema, more precisely defined as the edema of congestive heart failure, may be avoided or minimized by preoperative evaluation and therapy Failure to control the heart disease may constitute an absolute contraindication to surgical intervention If an operation is performed subsequent care is directed toward support of the crippled heart during the critical postoperative period

Intravenous Fluids The threat of pulmonary edema from overloading the circulatory system is of prime importance to the surgeon Extravagant use of physiologic saline solution is of particular importance in the development of pulmonary edema Vulnerability to intravenous indiscretions increases with age but also holds for the young and vigorous

Blood is the best substitute for blood If blood is not available, plasma is second best

The Wet Lung The entity of the traumatic wet lung has been described by Samson Burford and Brewer Whether this condition is the result of inability to cough or is a consequence of reflex bronchial spasm is of little practical importance Relief of pain and aspiration of the tracheobronchial tree will satisfy therapeutic requirements

Brian Blades M.D

trauma or disease If strong pleural adhesions are not present, pneumothorax will develop immediately In the case of large fistulas, tension pneumothorax may be rapidly fatal The emergency treatment is, of course, control of intrapleural pressure to prevent suffocation

Chronic Bronchopleural Fistula· Chronic bronchopleural fistula may be associated with empyema resulting from the rupture of a lung abscess into the pleura This will produce pyopneumothorax Leakage from the bronchial stump following pulmonary resection may produce a similar situation

Pyopneumothorax. The treatment of pyopneumothorax requires first, control of intrapleural pressures, and later adequate control of the infection It is important to emphasize that most bronchopleural fistulas heal if given time This is particularly true of deep fistulas which are not attached to the skin or chest wall Surgical intervention may be required if fusion to the thoracic wall prevents the circular contraction of the fistulous opening

Empyema· Empyema thoracis is now a rare disease Certain principles concerning its treatment, however, described by Graham, are of prime importance These are, briefly, that a true empyema is a collection of pus in the pleura, e g , an abscess If open drainage is established before the pneumonic process has subsided and before the lesion is a well walled off abscess, dangerous open pneumothorax will result The widespread use of the various antibiotics has almost eliminated the complications of pneumonia It is important to remember, however, that the availability of these drugs has not altered the basic principles in the management of empyema thoracis

Hypertrophic Pulmonary Osteoarthropathy· Clubbing of the fingers and toes may appear shortly after the onset of pulmonary disease It is seen frequently in untreated pulmonary suppurations of abscess and bronchiectasis Bronchogenic carcinoma, even without marked secondary infection may, however, cause clubbing of the digits The cause of this mechanism is unknown

Pulmonary Lobes, Segments and Lobules The lungs are divided into anatomical units of lobes which are usually fairly well defined Less easily identified, but definite structural units are the segments of the lobes and the lobular delineation of the segments Readers interested in the detailed anatomy of the lungs are referred to the excellent contributions of Miller, Brock, Huber, Boyden and others

Normally, there is a large reserve of lung tissue which furnishes a substantial factor of safety if pulmonary tissue must be extirpated or collapsed in the treatment of various diseases The removal of an entire

Chapter VII

CONTROL OF RESPIRATION

EFFICIENT functioning of the respiratory system will guarantee (1) an adequate oxygen supply and removal of carbon dioxide, (2) regulation of the hydrogen ion concentration in the blood, (3) part of the mechanism for control of body temperature, and, (4) excretion of body fluids The principal functions are, of course, the supply of oxygen and the removal of carbon dioxide from the blood

Chemical and nervous controls regulate these functions and maintain, under normal conditions, smooth and efficient respiratory exchange and pulmonary ventilation

Nervous Control Except under conditions of stress in which the accessory respiratory muscles are called into play, the nervous control of respiration is essentially reflex in nature The principal organs involved are the lungs and the respiratory muscles Since the motion of the lungs is chiefly dependent upon the action of the respiratory muscles, only the muscles themselves require motor nerve supply, which may be considered the efferent limb of the reflex arc controlling respiration These consist of the nerves to the muscles of the chest wall, the phrenic nerve to the diaphragm and the nerves to the abdominal and accessory muscles of the neck, which may play a part in the respiratory cycle

The Respiratory Centers The centers of the respiratory reflex arc consist of the motor cells of the anterior horn of the spinal cord and a higher center in the medulla which dominates central control If the spinal respiratory center, which does not have the ability to act automatically, is not able to receive impulses from the medullary center, spontaneous respiration will cease Division of the cervical cord above this spinal center will effect the phrenic and other respiratory nerves and be fatal There is however, no true spinal center in the anatomic sense or the physiological sense, since the anterior horn cells are *only* capable of mediating coordination of the respiratory muscles, but *do not* coordinate respiration

The Central Respiratory Center The central respiratory center has the ability to coordinate respiration by rhythmic *initiation of impulses* which cause the respiratory movements This center is func

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celeration of breathing maintains a normal respiratory rhythm and this reflex mechanism is known as the Hering Breuer reflex Sensory endings of the nerve are distributed in the lung and in the visceral pleura Exaggeration of the vagus reflex, which might be initiated by injury or disease stimulating the sensory ends will produce shallow and rapid breathing

Proprioceptive impulses from the respiratory muscles, including the diaphragm, act with the vagus afferent impulses to keep the respiratory center in balance Afferent fibers of muscle sense stimulate end organs in the muscles which transmit impulses to the medullary centers to inhibit inspiratory activity and allow the expiratory phase

Vago-Vagal Reflex Sudden fall in blood pressure and pulse with irregular or diminished breathing during the course of operations, and particularly operations within the thorax, have sometimes been attributed to the vago-vagal reflex Some observers believe that manipulations of the lung hilus in the region of the pulmonary nerve plexus account for the effects Infiltration of the nerves about the pulmonary hilum, with procaine has been suggested as a protective measure There may be such a mechanism, but it is safe to state that serious vago-vagal reflexes in the anesthetized human subject are rare The investigations of Bilfeldt Nicholls, Blades, Beattie and others indicate that the effects are the result of shifting of the mediastinum, or traction on the hilum of the lung, and are not the direct response of stimulation of the pulmonary plexus

The Phrenic Nerve The phrenic nerve, the chief innervation of the diaphragm has both motor and sensory fibers The exact stimuli which cause hiccoughing are unknown but these are, for the most part, transmitted over the afferent fibers of the phrenic nerve Certain pathologic conditions, however, may cause persistent hiccoughing and become serous and even result in death

Irritation of the phrenic nerve and the diaphragm may fire off the reflex which consists of sudden spastic contractions of the diaphragmatic muscles and associated respiratory muscles with violent suction of air past the glottis

Dilatation of the stomach peritonitis, inflammation of the diaphragm, aortic aneurysms and other lesions are frequently associated with hiccoughing.

There is no evidence from anatomical studies to indicate there are afferent branches of the phrenic nerve below the diaphragm It appears therefore that other afferent nerves may have the ability to set up the reflex which causes hiccoughing

tionally truly automatic since it initiates impulses which induce respiratory movements without regard to stimuli reaching it from other sources In addition to its own rhythmic activity, this center responds to stimuli from various afferent impulses and will alter activities when desirable It is, however, a reflex center For example, lack of oxygen or increase in carbon dioxide may make it necessary to call into play the accessory muscles or respiration Upon receiving these stimuli, the respiratory center will cause certain skeletal muscles to become more active than under normal conditions

The reflex system includes all of the afferent nerve fibers in the body which are capable of conducting sensory impulses to the medulla The response to these afferent impulses will depend upon the nature and vigor of the stimuli upon the center in the medulla itself

The exact anatomic position of the respiratory center in man cannot be defined precisely It is known, however, that these cells which control respiration lie close to the central end of the vagus nerves It is also established that the medullary center of respiration is bilateral and probably each half is able to control the respiratory movements on both sides of the body A still higher center has been postulated as being situated in the pons, which may have effect on breathing and perhaps some relation to the medullary center

Afferent Control of Respiration· Afferent impulses may be described in two groups First, those which are always present under normal circumstances and, in fact, account for smooth, normal respirations, and the second group which become active only under conditions of stress or strain These may set up a protective mechanism which tends to increase temporarily the speed and depth of respiration as compensatory mechanism

The normal afferent pathways include the afferent fibers of the vagus in the lungs and the nerve fibers of the muscle sense from the respiratory muscles Distention of the lungs on inspiration will stimulate the vagus endings in the organs which promote impulses to inhibit the action of the center, stopping short the inspiratory act and thus initiating expiration Other vagus endings are stimulated during the act of expiration which bring it to an end and will initiate the next inspiratory phase It is important to note, however, that division of the vagus afferent nerves will not cause cessation of respiration but breathing continues under the control of the respiratory center Under these circumstances, inspiration and expiration will be deeper and slower since the normal acceleration caused by stimulation of the vagus is interrupted

Herring-Breuer Reflex The action of the vagus nerves in the ac-

in the respiratory tree will cause coughing but not the violent type following laryngeal irritation

Carotid Sinus Respiration may be slowed by increased pressure in the carotid sinus through impulses to the medulla via the glossopharyngeal and vagus nerves Decrease in carotid sinus pressure will accelerate breathing

Spinal Nerves Afferent impulses through the spinal nerves, provoked by heat, cold or pain, may alter respiration sometimes causing gasping or holding of the breath The intensity, strength and frequency of the stimuli will determine the effects on the rate, rhythm and amplitude of breathing This mechanism may be protective, for example, momentary cessation of respiration following sudden immersion in water

Hiccough Hiccough is a respiratory reflex consisting of sudden spastic contraction of the diaphragm, and sometimes of the other respiratory muscles also, with suction of air past the just closing glottis A special center is improbable for such a peculiar reflex The afferent impulses are usually conveyed by afferent fibers in the phrenic nerve itself, but the adequate stimuli for eliciting the reflex are obscure

In some pathological conditions it is persistent and becomes of grave importance by affecting the general condition of the patient It occurs as a result of irritation of the phrenic nerve trunk, as in aortic aneurysm carcinoma of the root of the lung and affections of the diaphragm It occurs also in some cases of peritonitis and in diseases of the stomach, liver, kidney and adrenal Hence afferent nerves other than the phrenic probably can mediate the reflex since there are no anatomical data which indicate distribution of afferent phrenic fibers below the diaphragm to any of the abdominal organs Hiccough is believed to occur also from chemical effects upon the respiratory center in some cases of acidosis, acetonemia and venous stasis in the medulla A self-perpetuating "circus movement" type of nerve impulse in the medulla analogous to that in the heart in cardiac flutter and fibrillation, would seem to be a plausible explanation for the very persistent cases (Kubie, 1935) The extreme difficulty sometimes experienced in controlling the condition is pointed out by Weeks who cites cases from the literature in which even bilateral avulsion of the phrenic nerve failed to cure persistent hiccough In such instances the disorder apparently affects chiefly the respiratory muscles other than the diaphragm In many cases, however fluoroscopy will reveal that only one half of the diaphragm is at fault and crushing of the phrenic nerve on that side will cure the condition as in the case reported by Weeks

A central initiation of hiccoughing may originate in the respiratory center from acidosis or venous stasis There is no question that some central mechanism exists since hiccoughing may continue even after bilateral avulsion of the phrenic nerves

Occasional Afferent Regulators of Respiration· Afferent pathways to the respiratory center which become active only occasionally or under abnormal conditions include fibers from the higher parts of the brain and fibers in all of the cranial and spinal nerves Some examples may be mentioned The motor cortex, as a result of volitional activity may be a source of impulses which descend by way of the pyramidal tract to the respiratory center in the medulla and influence the center so as to alter the ordinary rhythm of breathing Such voluntary control of breathing may be conceived as a reflex, the cortex being looked upon as a "sensory end organ" emitting the impulse and the pyramidal tract from cortex to medullary center as the afferent pathway

Similarly, since emotional states are often accompanied by a change in respiration, as in crying or laughing, the fibers descending from the thalamus to the medulla may be considered as "afferent" pathways with respect to the respiratory center Pain is a subjective sensation which is particularly prone to affect breathing in this way, inducing rapid and shallow respiration The occurrence of yawning, which is essentially an atypical respiratory act, in cases of brain tumor can be explained by irritation of the brain resulting in "afferent" impulses to the medullary respiratory center, which modify its rhythmic activity Stimulation of the first cranial nerve (olfactory) by an odor can influence the respiratory center so as to induce sniffing or holding of the breath By stimulation of the second (optic) nerve a sight may "take one's breath away," that is, reflexly interrupt the normal respiratory rhythm The fifth cranial (trigeminal) nerve mediates sensation in the nasal mucosa, irritation of the latter can suddenly induce the modified respiratory act of sneezing One can readily conceive of circumstances under which auditory impulses might lead to gasping, holding the breath or some other modification of respiration The ninth cranial (glossopharyngeal) nerve mediates impulses from the pharynx which cause respiration to be suspended during the act of swallowing, so that the swallowed material will not be aspirated into the lungs as it passes over the opening of the larynx

The Cough Reflex Stimulation of the laryngeal branches of the vagus will set up afferent impulses which may cause violent stimulation of the respiratory center and cause coughing Vagus stimulation lower

been found that there are also chemical receptors in the root of the aorta which function in the same way as those in the carotid sinus Gesell (1939) reviews the evidence as to the relative importance of the medullary respiratory center and the carotid and aortic "centers" in responsiveness to chemical influences

Sodium cyanide acts upon the carotid bodies so as to produce respiratory stimulation This fact has been used by Smith, *et al*, as the basis of a method for determining the circulation time from various parts of the body to the carotid sinus The foot to-carotid time is increased postoperatively after the 4th day, and much more so than the arm to carotid time This slowing of the venous circulation they believe is probably an important factor in postoperative thrombosis and embolism

To illustrate how Gesell's theory harmonizes apparently discordant observations, the effects of oxygen lack may be mentioned When the body does not receive enough oxygen but the elimination of CO_2 is still adequate (as occurs at high altitudes due to the rarefied state of the air), increased breathing constantly occurs This cannot be due to CO_2 accumulation because there is no cause for the latter It cannot be due to increased acidity of the blood because the increased ventilation of the lungs washes out so much CO_2 that alkalemia is found on examining the blood, instead of acidemia

Gesell's theory attributes the increased breathing, in the presence of low CO_2 and decreased acidity of the blood, to an accumulation *in the cells of the respiratory center* of acid products of the metabolism of those cells, the oxidation of the acids being incomplete because of the inadequate supply of oxygen, for it is known that anoxemia always leads to accumulation of acid products in living tissues The interior of the nerve cells is more acid than normally at the same time that the blood bathing the cells is more alkaline than normally Presumably the same acid change occurs within the sensitive receptor cells of the carotid sinus

Oxygen Lack Oxygen lack does not often occur without a coincident CO_2 excess, hence it is not surprising that oxygen lack is more poorly adapted to stimulate breathing Oxygen lack is a less efficient respiratory stimulus than CO_2 excess for several reasons It increases the rate of breathing more than the depth, this is disadvantageous because the dead space air is a greater factor in rapid shallow breathing than in deep slow breathing It leads to washing out of CO_2 causing alkalemia, which tends to depress the respiratory center And it rapidly leads to decrease of the excitability and ultimate paralysis of the center

CHEMICAL CONTROL OF RESPIRATION

Attention may be confined to the medullary center in the discussion of the chemical control of breathing, since it appears that all the hormone regulation is effected through this center, no significant effect of chemical substances upon the spinal center or upon the respiratory organs themselves having been observed

Carbon Dioxide and Hydrogen Ion Concentration. It is well known that carbon dioxide, a product of metabolism, is the normal respiratory hormone It is a powerful respiratory stimulant, and it is evolved in amounts proportional to the rate of oxidation in the body, being thus well fitted to control the respiratory system, upon which the supply of oxygen depends

Other things being equal, the more CO_2 accumulates in a fluid the more acid becomes the reaction of the fluid, and it was thought at one time that CO_2 stimulated respiration only by increasing the hydrogen-ion concentration of the blood This belief was strengthened by the observation that injected lactic acid and other acids also stimulated breathing, though not to the same degree as an equivalent amount of CO_2 But this acid theory had to be modified when it was found that administered CO_2 stimulated respiration even if increased acidity of the blood was prevented by the simultaneous injection of an alkali It was then postulated that CO_2, because of its very great diffusibility across cell membranes, can penetrate into the nerve cells of the respiratory center more quickly than the less diffusible alkali, and thus can raise the hydrogen-ion concentration of the center itself even though the blood is at the time more alkaline than normally

This theory, advanced by Gesell (1925), holds that the real or ultimate chemical determinant of respiration is the hydrogen-ion concentration within the cells of the respiratory center itself, rather than the hydrogen-ion concentration of the blood It accords with all the known facts and is generally accepted at the present time, modified somewhat, however, by reason of the more recently acquired knowledge of the rôle played by the carotid sinus

Carotid Sinus and Aortic Chemical Receptors Heymans *et al* have shown that the carotid sinus region has chemical receptors, and when exposed to CO_2 excess or oxygen deficiency it responds in much the same way as the respiratory center itself, that is, it brings about an increase in respiration In effect, it serves as a subsidiary respiratory center The oxygen-lack stimulus is in fact more effective in the carotid sinus than it is in the respiratory center Carbon dioxide's action, however, is greater in the medullary center than in the carotid sinus It has

very low blood pressure in some cases of anemia, as for example after severe hemorrhage, have a tendency to cause confusion with regard to the oxygen tension of the blood They might seem at first to be in compatible with normal oxygen tension, but on more accurate analysis it becomes clear that there is no connection between these different factors The oxygen tension in the arterial blood depends only on the proper exposure of the latter to a suitable tension of oxygen in the alveolar air, it is wholly independent of the quality of the blood (e g, anemia) or the mechanical conditions of the circulation (e g, shock)

Deficient Pressure of Oxygen Decreased tension of oxygen in the blood occurs in all types of respiratory obstruction, such as tracheal occlusion by a foreign body or blocking of a bronchus by a mucus plug In these cases the oxygen tension of the air in the blocked alveoli is lower than normal and the blood cannot possibly obtain oxygen under a higher pressure than that present in the alveoli

The respiratory center and its outposts, the carotid sinus and aortic receptors are much more sensitive to diminished oxygen tension than to a decrease in the amount of oxygen received per minute The former condition is a more effective stimulus and induces a greater increase in pulmonary ventilation Common clinical observations support this principle In acute hemorrhage as for example in ruptured ectopic gestation, there is often some degree of air hunger so-called, but there is never the extreme respiratory activity which occurs at the onset of massive collapse of the lung or of acute pneumothorax In the latter conditions the blood leaving the intact parts of the lungs is normally oxygenated but is joined by unaerated blood from the non functioning parts with the result that the oxygen tension of the mixed arterial blood is reduced

When the respiratory center is depressed and suffering from anoxia the administration of oxygen in high concentration results in further respiratory depression or even apnea and respiratory failure Burstein cites evidence that this adverse effect occurs only when the carotid sinus and aortic receptor mechanisms are functionally active When the respiratory center in the medulla is depressed oxygen lack serves as a stimulus to the sino-aortic mechanism and thereby maintains respira tory activity if under these circumstances oxygen is administered so as to remove the "anoxemia stimulus" the sino-aortic mechanism ceases to act and, the medullary respiratory center being depressed apnea re sults Whereas anoxemia is a respiratory stimulus in the intact organism it causes only depression of respiration if the carotid sinus and the aortic arch have previously been denervated

because anoxemia depresses the vitality of the latter This does not contradict the statement made above that anoxemia stimulates respiration It is a general principle that any stimulus becomes a depressant when it exceeds a certain limit It is obvious that when any of the cells of the body are deprived of oxygen entirely they cannot survive From the time the deprivation occurs the cells may be considered as undergoing the process of dying At the beginning of this process they are in a fairly healthy condition, and capable of responding to the acid products which accumulate within them But as oxygen lack continues the health and therefore the responsiveness of the cells must steadily become impaired Nerve cells have particularly poor resistance to oxygen deprivation, and the depression of the respiratory center by anoxemia is merely a stage in the process of actual disorganization of the cellular mechanism

There are two different types of oxygen lack, namely (1) decrease in the *amount* of oxygen supplied per minute, and (2) decrease in the *pressure* under which the oxygen is supplied The distinction between these two conditions, which is of practical importance, can be made clear by clinical examples

Deficient Amount of Oxygen In a case of surgical shock the lungs may be perfectly normal, the movements of respiration practically unimpaired and the hemoglobin content of the blood quite high Under these circumstances the alveolar oxygen pressure is normal and the pulmonary blood becomes saturated with oxygen under normal pressure since it is brought into equilibrium with the alveolar oxygen pressure Moreover each cubic centimeter of blood acquires at least the normal amount of oxygen, since there is plenty of hemoglobin present to carry the oxygen The element of oxygen lack in the respiratory center and other tissues depends therefore entirely on the slowness with which this well oxygenated blood circulates through them All the oxygen which does reach the respiratory center and carotid sinus, though less in *amount* than normally, is under normal tension, that is, the tension with which its was forced into the blood from the alveolar air across normally permeable alveolar walls

In anemia, likewise, the oxygen tension of the blood is normal for the same reason, the blood is exposed to unhindered equilibration with normal alveolar air across normal alveolar walls But in anemia the amount of oxygen per cubic centimeter of blood is less than normal because of diminished carrying capacity Hence the respiratory center may not receive enough oxygen per minute, though that which it does receive is under a sufficiently high pressure The marked pallor and

conditions the ventilation of the lungs is regulated according to other needs of the body, namely, regulation of blood reaction or body temperature, or elimination of water These sustained adaptations are effected mainly by means of chemical control of respiration

It should be understood that the really essential measure of respiratory adequacy is not either the rate of breathing or the depth of each breath, but the per minute *total ventilation* of the lungs Frequently in clinical usage notice is taken only of the rate of breathing, but this is only because the rate can be measured easily and accurately and the depth cannot As Henderson states, measurement of respiration—in the sense of the volume of air breathed in liters per minute—is quite as important as a guide to prognosis and treatment in many disorders as is measurement of arterial pressure He considers the lack of apparatus for measuring this factor of respiration one of the greatest deficiencies in medical technique A continuous measurement of the per minute ventilation of the alveoli, which is the factor of prime importance, is impossible in practically all clinical conditions, hence it is that undue emphasis is often placed on the rate of breathing alone The rate of respiration should always be interpreted with reference to the total volume of air supplied to the alveoli per minute, that is, the latter should be estimated approximately by taking into account the average depth of the breaths taken, as estimated from inspection of the respiratory excursions of the thorax

APNEA

Nervous Apnea Apnea may be nervous or chemical in origin Nervous apnea may be produced by interference with the nervous control of breathing at any part of the reflex mechanism In fracture of the upper cervical spine or in anterior poliomyelitis all the *efferent* fibers may be thrown out of function Intracranial lesions may cause paralysis of the *medullary center* Abnormal stimulation of various *afferent* nerve fibers, particularly those of the vagus, may induce respiratory arrest lasting a certain length of time, that is, reflex apnea. The rather prolonged apnea which often occurs immediately after tracheal intubation is a familiar example In general such reflex apnea is of little clinical importance, for *the chemical control of breathing predominates over the nervous control* to such a great extent that breathing is practically always resumed before the reflex apnea results in any dangerous degree of anoxia For example, in the induction stage of ether anaesthesia holding the breath is common, due to stimulation of afferent nerves by the irritant ether vapor As a result of this apnea CO_2 ac

Carbon Dioxide Excess If the inspired air contains 6 per cent CO_2, headache and mental confusion are likely to result With continued breathing of still higher percentages the breathing gradually becomes slower and finally ceases due to the toxic effect of the substance upon the respiratory center in such high concentrations Shute and Davis employed 30 per cent CO_2 with 70 per cent O_2 for stimulation of respiration in morphine narcosis in the newborn This mixture cannot safely be given for more than a very short period CO_2 excess in inspired air causes such severe choking sensations that accidental CO_2 poisoning cannot occur in a conscious person, but too high a concentration of CO_2 may be given to patients under anaesthesia by mistake or by allowing too much rebreathing with the closed method It is true that CO_2 diffuses through rubber fairly rapidly, but not nearly as fast as it is exhaled into the anaesthesia apparatus by the patient

Per Minute Ventilation of the Lungs Whereas many reflexes affect respiration rather transiently (e g , sneeze, cough) and alter mainly the rhythm of breathing in some way, the chemical control effects the more prolonged adaptations of the respiration, and influences particularly the *total ventilation* of the lungs *per minute,* rather than the rate or rhythm

It is important to distinguish between stimulation of breathing and acceleration of breathing The former means an increase in the volume of air actually ventilating the alveoli per unit time An increased rate of breathing may or may not connote an increased alveolar ventilation, depending upon whether or not the depth of breathing changes A respiratory stimulant in the true sense is that which increases the total alveolar ventilation, regardless of its effect upon the rate of breathing In fact, stimulation of breathing may be associated with an actual slowing of the rate. For example, pleural pain often causes shallow rapid breathing by reflexly inhibiting each phase of respiration before it progresses very far Administration of the powerful stimulant CO_2 in such a case often stimulates the medullary center so strongly that the latter is no longer disturbed or checked by the pain impulses, and induces a very deep and effective type of breathing with an actually slower rate than that which was present before It has been pointed out above that deep slow breathing is more efficient than shallow rapid breathing, and carbon dioxide, the normal respiratory determinant, definitely increases the depth of breathing more than the rate, sometimes even decreasing the rate in favor of an increase in depth

Total ventilation of the lungs per minute must be proportional to the metabolic rate if the oxygen supply is to be adequate, and this may be considered the prime function of external respiration But under certain

tone of the vasomotor center and perhaps also impairs the effectiveness of cardiac contraction Boothby *et al* state that 100 per cent oxygen can be administered to patients for as long as 48 hours without causing pulmonary irritation They mention a few indications for such administration

Apnea from Anoxemia Though oxygen lack of moderate grade stimulates breathing severe oxygen lack depresses the respiratory center and eventually paralyzes it, causing apnea Apnea from this cause is a grave condition, in fact is soon fatal if not relieved, because the chemical changes which occur in the cells of the respiratory center after a certain period of anoxia are irreversible

Apnea from Drugs Chemical apnea is frequently caused by exogenous substances particularly anesthetic and preanesthetic drugs, which directly depress and ultimately paralyze the respiratory center The chief therapeutic problem in this type of apnea is one of elimination Therefore the classification of anesthetic agents as volatile and non volatile is of practical importance In apnea due to an overdose of ether or ethylene, artificial respiration both relieves the apnea and eliminates its cause simultaneously Apnea due to morphine or the barbiturates on the contrary is more serious in that there is no way of causing rapid elimination or destruction of the depressant

'Physiological Condition' of Respiratory Center A factor of constant importance in connection with apnea is the "physiological condition" of the respiratory center This term refers to a great number of separate factors which definitely determine a predisposition or susceptibility to respiratory depression or paralysis Age, malnutrition, dehydration, hemorrhage, toxemia are some of the more obvious factors which may impair the physiological condition of the respiratory center as well as of the other tissues of the body However there are many other less conspicuous conditions which may influence the vitality of the respiratory center, such as the acid base balance the concentrations of the various specific ions of the blood the recent history of the individual with respect to physical training and possibly endocrine factors One factor of practical importance which is often neglected is fatigue of the respiratory center related to chronic respiratory obstruction from any cause In partial obstruction of the respiratory passages as by thyroid enlargement aneurysm or new growth there is continuous compensatory overaction of the respiratory center which in the course of time damages the center and in some manner renders it more vulnerable to depressants particularly morphine

Apnea Test in Thyrotoxicosis The duration of voluntary apnea in

cumulates and oxygen lack develops, so that the respiratory center is soon powerfully stimulated by the combined action of both these factors This chemical stimulation easily predominates over the reflex inhibition, and breathing is resumed in spite of the latter

Chemical Apnea *Deficiency of Carbon Dioxide* Chemical apnea is a matter of more importance It can result from lack of adequate chemical stimulation of a normal respiratory center, or from depression of the center by an abnormal chemical environment The normal adequate stimulus for continued breathing is a proper concentration of CO_2 in the blood and respiratory center Simple hyperventilation of the lungs for a short time removes this stimulus and induces apnea Such hyperventilation and washing out of CO_2 may occur in connection with the early stages of anaesthesia because of psychic or other factors, and it is possible for the depressing action of the anaesthetic agent itself to take effect just at a time when the normal stimulating factor is at a low level, with dangerous results

"Excess of Oxygen" It has been mentioned above that oxygen lack stimulates respiration The question therefore arises as to whether oxygen excess, as for instance from overbreathing or administration of pure oxygen can depress respiration and cause apnea It cannot, chiefly because it is impossible to supply a large excess of oxygen to the respiratory center, since the blood is almost fully saturated with oxygen by ordinary quiet breathing of atmospheric air Increased ventilation of the lungs or higher concentrations of inspired oxygen can only raise the tension of oxygen in the blood (and hence in the respiratory center) about 5 per cent at most The quantity of oxygen available to the center, as distinguished from the oxygen tension, does not affect breathing, for the center, like other living tissues, uses only as much oxygen as it needs Of course, voluntary apnea can be maintained longer if the lungs are filled with oxygen at the start, also apnea due to washing out CO_2 by overbreathing will persist longer if the alveolar air is enriched with oxygen at the start of the apnea In these cases, however, the extra amount of oxygen stored in the lungs serves only to sustain the apnea, by postponing the time at which oxygen lack becomes marked enough to cause resumption of breathing The stored oxygen does not of itself induce the apnea

"Oxygen Poisoning" Voluntary overbreathing often is followed by a fall in blood pressure, faintness and other symptoms which are sometimes ascribed to "oxygen poisoning" These symptoms, however, are in no way dependent on oxygen excess They result from abnormally rapid loss of CO_2, the rapid decrease in the CO_2 tension of the blood inhibits the

however, the CO_2 concentration is found by actual measurement to be still below the normal threshold for stimulation, hence it is the oxygen lack which is responsible for the return of breathing As soon as breathing starts, both stimuli are made weak again, for the oxygen lack is relieved, and CO_2 is washed out As a result, a second period of apnea follows There occur therefore alternating periods of breathing and apnea until the concentration of CO_2 finally becomes great enough to predominate over the lack of oxygen as the respiratory determinant The sequence of events may be indicated in Table II

Treatment of Apnea *Nervous Apnea* The proper treatment of apnea depends upon the cause of the condition, more specifically upon whether the apnea is of the nervous or chemical type, or a combination of the two Reflex apnea such as occurs for example immediately after the introduction of a tracheal tube, usually requires no special treatment, since breathing is soon restored by the normal chemical mechanism operating on the inhibited but otherwise undamaged respiratory center It is only in this type that sensory stimulation, as by striking the surface of the body applying heat or cold, or dilating the anal sphincters, may hasten the return of breathing appreciably But there is hardly any rational basis for the application of these or other kinds of trauma even in reflex apnea, for the latter will always cease spontaneously within a short time and if for any reason it is thought that the patient should be supplied with oxygen at an earlier moment and not be allowed to await the return of automatic breathing *artificial respiration* is a sure and a more dignified means of attaining this object

Chemical Apnea In chemical apnea the respiratory center not only has ceased to act but is depressed or actually damaged by some noxious substance which must be removed, or as the result of some other unfavorable chemical circumstances such as anoxemia, fatigue, dehydration, inanition The prime indication in chemical apnea of all kinds is *artificial respiration,* not medicine Henderson, in a comprehensive article on resuscitation, emphasizes this fact, even stating that "all subcutaneous, intravenous or intracardiac medication is harmful rather than beneficial in asphyxia" Many authorities are of the opinion however that subordinate to artificial respiration there is also a place for certain respiratory stimulant drugs

thyrotoxicosis has been studied by Bartlett as a possible index of toxicity and a criterion of operative risk He found that in thyrotoxicosis the ability to hold the breath is decreased in both the inspiratory and expiratory phases in a characteristic manner The ultimate basis for this fact is uncertain, but the "physiological condition" of the respiratory center is probably a factor

Periodic Breathing Periodic breathing generally is indicative of severe depression of the respiratory center, bordering on respiratory failure Many physiological mechanisms exhibit such intermittent activity just before they fail completely When a person supports a heavy weight in his hand with arm outstretched, as the muscles become fatigued they do not lose their power gradually and steadily, nor do they show the full effects of fatigue all at once and permit the weight to drop suddenly Instead, the hand falls and recovers a number of times before fatigue finally becomes so profound that the weight cannot be lifted at all

Periodic breathing occurs whenever oxygen lack acts as the effective respiratory stimulus instead of the CO_2 concentration, either by reason of the severity of the former or a marked diminution of the latter For example, voluntary hyperventilation reduces the CO_2 concentration of the blood and thereby induces apnea During the period of apnea, oxygen lack becomes more and more marked, and also, the CO_2 concentration rises again toward normal Both of these factors tend to stimulate breathing, and soon breathing is resumed At that moment,

TABLE II

PERIODIC BREATHING FOLLOWING HYPERVENTILATION

	Normal	*Hyperventilation*	*Apnea*	*Respiration Resumed*	*Apnea*	*Respiration*	*Normal*
Alveolar O_2 tension (mm Hg)	100	140	30	50	40	etc , approaches	100
Alveolar CO_2 tension (mm Hg)	40	15	35	30 Because of both factors	37 Because both stimuli are weakened	etc , approaches	40

does not imply that the oxygen occupies a certain known volume in the blood Actually the oxygen exists in a contracted state in the blood chiefly in chemical combination with hemoglobin, its volume means the volume when liberated and measured as a gas The percentage of oxygen in the solid tissues such as muscle cannot be stated because it is difficult to measure the volume of such tissues accurately, and the oxygen content is constantly fluctuating according to the degree of activity of the tissues and the rate of blood flow through them The figure is of no practical value for these same reasons, the tension of the oxygen is the important factor

Coefficient of Utilization Arterial blood contains normally about 20 cubic centimeters of oxygen per 100 cubic centimeters of blood (0 3 cubic centimeter in solution 19 7 cubic centimeters in chemical combination with hemoglobin) Venous blood contains about 15 cubic centimeters of oxygen per 100 cubic centimeters during rest and a smaller amount during activity The difference between the oxygen content of arterial blood and that of venous blood (5 cubic centimeters) represents the oxygen utilized in the tissues When it is compared to the amount of oxygen available to the tissues (20 cubic centimeters), it is found to amount to 25 per cent of the latter This figure is the "coefficient of utilization," that is the percentage of the total arterial oxygen removed during the passage of the blood through the tissues

Chemical Factors in Oxygen Exchange The only factor responsible for the transfer of oxygen from the arterial blood (O_2 tension 100 millimeters Hg) to the tissues (O_2 tension 20 to 0 millimeters Hg) is the difference in oxygen pressure as mentioned above

However there are certain other factors which facilitate this transfer, by assisting in the dissociation of oxygen from oxyhemoglobin One is the increase of CO_2 The higher the *tension of* CO_2 the more it facilitates the dissociation of HbO_2 Since the tension of CO_2 is highest in the tissues, for that is where the gas is evolved, liberation of oxygen from the blood is most favored just where oxygen is most needed At the lungs the mechanism is reversed the sudden drop in blood CO_2 tension resulting from diffusion of CO_2 from the blood into the alveoli restores the oxygen-carrying capacity of the hemoglobin to its previous level Acid substances in general have the same effect as CO_2 upon the oxygen association power of hemoglobin, the effect may therefore be attributed to alterations of *H ion concentration* from whatever cause

It is to be expected that other acid products of metabolism besides CO such as lactic acid will have their highest concentration in the

CHEMISTRY OF RESPIRATION

OXYGEN EXCHANGE

Physical Factors in Oxygen Exchange The transfer of gases which occurs in the lungs and in the tissues is dependent on physical differences in pressure rather than upon chemical factors Both for oxygen and for carbon dioxide there is a series of pressure gradients, corresponding to the various points at which transfer of these gases takes place, which determine the direction of movement In the case of oxygen, the source is the atmospheric oxygen which exists under a pressure equal to about 20 per cent of the total atmospheric pressure, that is, about 152 millimeters Hg Oxygen from the air is carried by inspiration into the alveoli where the oxygen pressure is lower, being only 105 millimeters Hg, about 14 per cent of the total alveolar gas pressure

This alveolar oxygen pressure represents a balance between respiratory renewal and circulatory removal of the gas Alveolar oxygen is transferred to the arterial blood, bringing the oxygen pressure of the latter nearly up to, but never above, that in the alveoli, that is to about 100 millimeters Hg The arterial blood gives up oxygen to resting tissues because the oxygen pressure in the latter is much lower than 100 millimeters Hg, averaging perhaps 20 millimeters Hg It liberates oxygen more rapidly to active tissues because the latter consume oxygen so fast that their oxygen pressure is kept lower, even near 0 millimeter Hg in very active muscle In passing through the tissues the blood oxygen tension does not come into complete equilibrium with that of the tissues The venous blood therefore retains enough of the arterial oxygen to have an average oxygen pressure of about 40 millimeters Hg, this figure varying of course with different degrees of activity The venous blood, with 40 millimeters Hg oxygen tension, when exposed to the alveolar oxygen tension of 105 millimeters Hg is recharged with oxygen up to 100 millimeters Hg pressure

Oxygen in Gases, Fluids and Solids The percentage of oxygen means simply the percentage by volume in the gaseous state in the case of the atmospheric air (20 94 per cent O_2) and alveolar air (about 14 per cent O_2) The "percentage" of oxygen in the blood means, of course, the volume of oxygen contained in 100 cubic centimeters of blood *if* that oxygen were liberated and its volume measured under standard conditions in the gaseous state

This comparison of gas and fluid on the basis of volume percentage

does not imply that the oxygen occupies a certain known volume in the blood Actually the oxygen exists in a contracted state in the blood chiefly in chemical combination with hemoglobin, its volume means the volume when liberated and measured as a gas The percentage of oxygen in the solid tissues such as muscle cannot be stated because it is difficult to measure the volume of such tissues accurately, and the oxygen content is constantly fluctuating according to the degree of activity of the tissues and the rate of blood flow through them The figure is of no practical value for these same reasons, the tension of the oxygen is the important factor

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It is to be expected that other acid products of metabolism besides CO such as lactic acid will have their highest concentration in the

most active tissues, and there reinforce the effect of CO_2 on the dissociation of oxyhemoglobin

Increase of *temperature* renders hemoglobin less capable of holding oxygen It is conceivable that even under resting conditions this factor plays some part in the body, for the blood is ordinarily exposed to the lowest temperature in the lungs and to the highest temperature in the tissues, where all the heat of the body is produced

The total *concentration of electrolytes* in the surrounding medium, apart from the action of any specific ion affects the oxyhemoglobin combination, the higher the concentration of electrolytes the greater the tendency to liberate oxygen This factor is at its maximum in the tissues and therefore is an accessory factor in the release of oxygen from the blood.

The *concentration of hemoglobin* itself has some influence upon the ease with which it dissociates oxygen, the higher the concentration of hemoglobin, the more readily does it liberate oxygen In marked anemia the actual disturbance of oxygen exchange may therefore be greater than the reduction in hemoglobin content of the blood would indicate

Oxygen Dissociation During Exercise During rest the coefficient of utilization of oxygen is about 25 per cent, as a result of the various factors just mentioned The coefficient rises during activity, and in violent exertion may reach 80 per cent This means that each 100 cubic centimeters of blood actually supplies to the tissues over three times as much oxygen as during rest, in fact, does more than three times as much work This alteration of the dissociability of oxyhemoglobin reduces very markedly the burden on the circulation, for if the coefficient of utilization did not increase with exercise, the heart would have to increase its pumping action in equal proportion to every increase in the rate of exercise

A number of factors, including those enumerated above which control liberation of arterial oxygen during rest, are responsible for the greater availability of the arterial oxygen to the tissues in exercise The oxygen gradient between the arterial blood and the tissues is steeper during exercise because the oxygen tension in active muscles approaches zero due to the more rapid rate of consumption of the oxygen The arterial oxygen tension of 100 does not change appreciably, regardless of any increase in ventilation of the lungs, for it is entirely dependent on alveolar oxygen tension and the latter is prevented from rising much above its usual level of 105 because of the large amounts of CO_2 constantly poured into the alveoli from the venous blood The normal

effects of CO_2 tension and of hydrogen ion concentration on oxygen dissociation are augmented during activity because of increased CO_2 production Likewise the temperature rise in the tissues when they become active is probably of sufficient magnitude to accelerate the reaction appreciably The greatest factor of all is the opening of addi

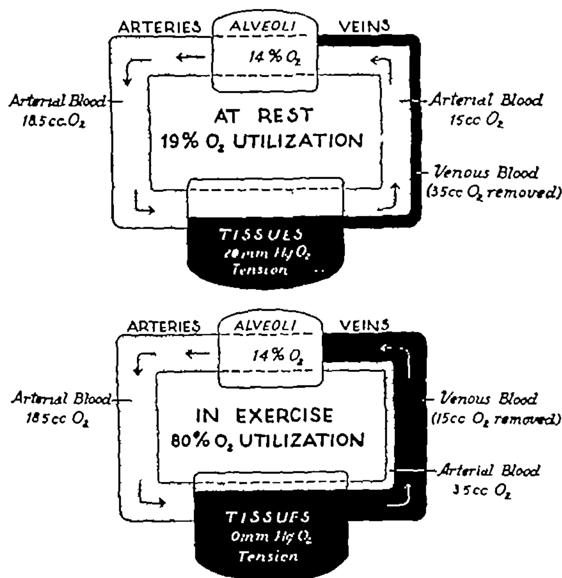


FIG. 17 Coefficient of utilization of oxygen at rest and in exercise

tional tissue capillaries with consequent increase in the total surface available for oxygen transfer (Figure 17)

The pressure relations in the oxygen cycle during rest and exercise are summarized briefly in the following table The percentages of oxygen at the various parts of the cycle are added for convenient reference

most active tissues and there reinforce the effect of CO_2 on the dissociation of oxyhemoglobin

Increase of *temperature* renders hemoglobin less capable of holding oxygen It is conceivable that even under resting conditions this factor plays some part in the body for the blood is ordinarily exposed to the lowest temperature in the lungs and to the highest temperature in the tissues where all the heat of the body is produced

The total *concentration of electrolytes* in the surrounding medium, apart from the action of any specific ion affects the oxyhemoglobin combination the higher the concentration of electrolytes the greater the tendency to liberate oxygen This factor is at its maximum in the tissues and therefore is an accessory factor in the release of oxygen from the blood

The *concentration of hemoglobin* itself has some influence upon the ease with which it dissociates oxygen the higher the concentration of hemoglobin the more readily does it liberate oxygen In marked anemia the actual disturbance of oxygen exchange may therefore be greater than the reduction in hemoglobin content of the blood would indicate

Oxygen Dissociation During Exercise During rest the coefficient of utilization of oxygen is about 25 per cent, as a result of the various factors just mentioned The coefficient rises during activity, and in violent exertion may reach 80 per cent This means that each 100 cubic centimeters of blood actually supplies to the tissues over three times as much oxygen as during rest in fact, does more than three times as much work This alteration of the dissociability of oxyhemoglobin reduces very markedly the burden on the circulation, for if the coefficient of utilization did not increase with exercise the heart would have to increase its pumping action in equal proportion to every increase in the rate of exercise

A number of factors, including those enumerated above which control liberation of arterial oxygen during rest, are responsible for the greater availability of the arterial oxygen to the tissues in exercise The oxygen gradient between the arterial blood and the tissues is steeper during exercise because the oxygen tension in active muscles approaches zero due to the more rapid rate of consumption of the oxygen The arterial oxygen tension of 100 does not change appreciably, regardless of any increase in ventilation of the lungs, for it is entirely dependent on alveolar oxygen tension, and the latter is prevented from rising much above its usual level of 105 because of the large amounts of CO_2 constantly poured into the alveoli from the venous blood The normal

pure solution of hemoglobin with oxygen when the solution is exposed to increasing tensions of oxygen This may be called the *oxygen association curve of hemoglobin,* though the term oxygen-dissociation curve is used more commonly, because it is easier experimentally to start with hemoglobin fully saturated with oxygen and measure the oxygen loss on reducing the oxygen pressure in successive steps The shape of the curve is dependent upon the inherent chemical nature of hemoglobin with regard to its tendency to combine with oxygen If the taking up of oxygen were a matter of simple physical solution instead of a complex and delicate chemical reaction, the increments of oxygen would be directly proportional to the changes in tension and the graph would be a straight line

Influence of Temperature Electrolytes and Carbon Dioxide The influence of the various factors mentioned above upon the oxygen combining power of hemoglobin may be illustrated by their effect upon this oxygen association curve A given factor, temperature for instance, may alter the reaction markedly at one part of the curve, that is at certain tensions of oxygen, but disturb it very little at other parts Curve B indicates that hemoglobin is capable of holding less oxygen at a higher temperature than at a lower one This fact is of physiological import in that the temperature is higher in the tissues than in the alveoli Curve C shows that the presence of electrolytes lowers the oxygen capacity of hemoglobin Curve D shows that the presence of a certain pressure (20 millimeters) of CO_2 decreases the ability of hemoglobin to hold oxygen, compared with say, 10 millimeters CO_2 pressure, and curve E that a higher pressure (40 to 46 millimeters) of CO_2 has a correspondingly greater effect

Influence of Changes in CO_2 Tension However curve E is a somewhat more complicated matter as might be expected since it represents something closer to real life It represents the oxygen-capacity of hemoglobin when influenced by body temperature by the presence of salts and by the presence of a relatively high CO_2 tension namely about 40 millimeters Hg But the last factor is not constant at all parts of the curve the CO tension has been maintained at 46 millimeters Hg in connection with the lower oxygen tensions that is up to about 40 millimeters Hg O and lowered to 40 millimeters Hg CO_2 for the rest of the curve

It is apparent that this alternation in the CO_2 tension simulates what occurs in the body for in the tissues and in the venous blood the oxygen tension is low the CO_2 tension high, while in the arterial blood the oxygen tension is high and the CO_2 tension lower This change of 6

TABLE III

PRESSURES AND VOLUME-PERCENTAGES OF OXYGEN IN THE RESPIRATORY CYCLE

	Atmospheric Air	*Alveolar Air*	*Arterial Blood*	*Tissues*	*Venous Blood*
O_2 tension mm Hg	152	105	100	20–0	40 (about)
O_2 volumes per cent	20	14	(20 cc)		(15 cc)

Oxygen Transport by the Blood· *Rôle of Hemoglobin* When a pure solution of hemoglobin is exposed to gradually increasing pressures of oxygen, the hemoglobin takes up increasingly greater amounts of oxygen but not directly in proportion to the pressure At very low oxygen tensions hemoglobin readily takes quite large amounts of oxygen, then as the tension is increased the hemoglobin accepts smaller and smaller increments of oxygen in combination as the saturation point is approached

This property of hemoglobin is illustrated in Figure 18 by the Curve A, which represents the successive degrees of saturation of a

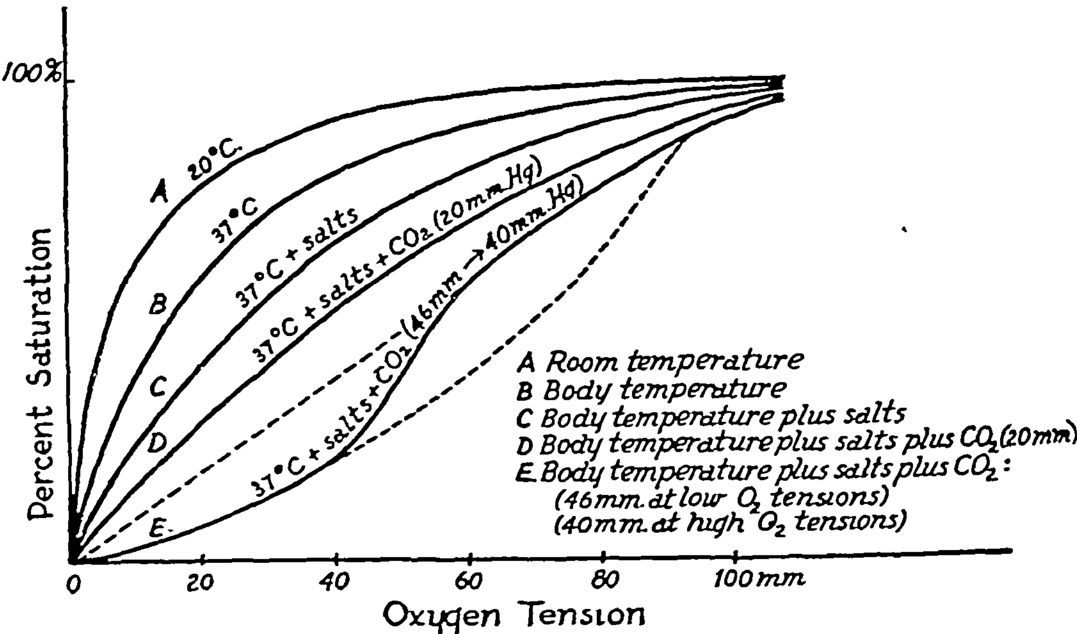


FIG 18 Oxygen association curves of hemoglobin, the successive degrees of saturation with oxygen of a hemoglobin solution when exposed to increasing tensions of oxygen

occur because the alveolar air is not directly in "contact" with atmospheric air

The opportunity for diffusion depends entirely upon the rate of ventilation of the alveoli, with atmospheric air, and this rate does not become rapid enough to permit the alveolar CO_2 tension to fall below 40 millimeters Hg

The respiratory center strives to maintain the alveolar CO_2 pressure permanently at about 40 millimeters and has the power to do so The *respiratory center is always kept informed as to the alveolar* CO_2 tension because the arterial blood constantly arriving at the center has left the lungs only a moment before, where it was fully exposed to and equilibrated with the alveolar air and therefore has the same CO_2 tension as the latter If the alveolar CO_2 tension for any reason rises above 40 millimeters Hg, the arterial blood CO_2 tension is correspondingly raised and promptly informs the respiratory center The latter immediately becomes more active, for nothing stimulates it better than a little extra CO_2 in its blood supply The result is increased ventilation of the alveoli with practically CO_2-free air, reduction of the alveolar CO_2 tension to the desired level of 40 millimeters Hg, corresponding fall of the arterial CO_2 tension to match the alveolar CO_2 tension, loss of the added respiratory stimulus and resumption of the ordinary rate of ventilation

In an analogous manner diminished alveolar CO_2 tension leads to decrease or complete cessation of alveolar ventilation and restoration thereby of the normal tension of 40 millimeters Hg The most important fact in connection with this mechanism is that the tension of CO_2 and in fact of any gas in the arterial blood is practically the same as the tension of the same gas in the alveolar air This is naturally the case,

TABLE IX

PRESSURES AND VOLUME PERCENTAGES OF CARBON DIOXIDE IN THE RESPIRATORY CYCLE

	Atmospheric Air	*Alveolar Air*	*Arterial Blood*	*Tissues*	*Venous Blood*
CO_2 tension mm Hg	0 2	40	40	60	46
CO_2 volumes per cent	0 03	5 6	53	—	55–60

millimeters Hg in the CO_2 tension has the effect of making the oxygen-association curve of hemoglobin distinctly S-shaped This signifies that the fact that hemoglobin holds much less oxygen after passage through the tissues than it does after passage through the lungs is only partly due to the lower oxygen tension to which it is exposed in the tissues (20 millimeters Hg O_2) as compared with that in the alveoli (105 millimeters Hg O_2), an important additional reason is the seemingly rather slight difference in CO_2 tension in the two regions, 46 millimeters Hg in the tissues and 40 millimeters Hg in the alveoli

The carbon dioxide cycle in the body is thus harmoniously linked with the oxygen cycle, rhythmically facilitating the formation of oxyhemoglobin in the lungs and the dissociation of oxyhemoglobin in the tissues

CARBON DIOXIDE EXCHANGE

Physical Factors in Carbon Dioxide Exchange. The source of the carbon dioxide of the body is the tissue cells, which elaborate it at a rate determined by metabolic activity The CO_2 tension in the tissues is about 60 millimeters Hg during rest The carbon dioxide constantly diffuses into the capillary blood vessels, producing a CO_2 tension of 46 millimeters Hg in the venous blood leaving the tissues In the lungs this blood is exposed to alveolar air whose CO_2 tension is 40 millimeters Hg The blood gives off CO_2 to the alveolar air until it becomes equilibrated with the latter, hence arterial blood as it leaves the lungs has still a considerable CO_2 tension, 40 millimeters Hg When this blood again passes through the tissues its CO_2 tension is again raised to 46 millimeters Hg by diffusion into it of CO_2 from the region of higher pressure, namely the tissues (60 millimeters Hg)

The CO_2 pressure-difference of 6 millimeters Hg between venous blood (46 millimeters) and alveolar air (40 millimeters) is very small compared to the oxygen pressure difference of 65 millimeters between alveoli (105 millimeters) and venous blood (40 millimeters) Yet the smaller CO_2 gradient is ample to maintain adequate transfer of the gas because of the exceptionally great diffusibility of CO_2 and its marked solubility in the diffusion membranes (capillary and alveolar walls) and in the body fluids Some CO_2 gradient is always maintained because CO_2 is continuously being evolved in the tissues

The CO_2 tension of atmospheric air is practically zero The 40 millimeter CO_2 pressure in alveolar air might be expected to fall markedly as a result of diffusion of CO_2 into the atmosphere, but this does not

of the carbon dioxide reacts directly with the basic amino ($—NH_2$) groups of the protein hemoglobin, to form carbamino compounds (Hb NH COOH)

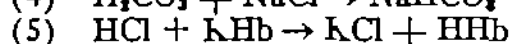


$$(3)\quad HbNH_2 + CO_2 \rightarrow HbNHCOOH$$

Indirect Hemoglobin Transport The indirect transport of CO_2 by hemoglobin depends upon the fact that the basic ions Na and K cannot pass freely across the red cell membrane, whereas the acid radical Cl can pass freely in either direction The plasma contains a preponderance of sodium while the chief basic radical within the cells is potassium. The undue acidity of the plasma which would otherwise result from the continuous accession of CO_2 is offset by passage of chloride into the red cells, where it reacts with the potassium bound to hemoglobin In this way the hemoglobin indirectly increases the CO_2 capacity of the blood

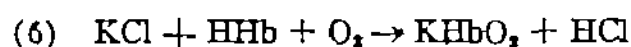


$$(4)\quad H_2CO_3 + NaCl \rightarrow NaHCO_3 + HCl$$

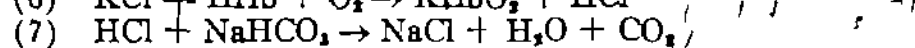


$$(5)\quad HCl + KHb \rightarrow KCl + HHb$$

As in the case of reaction (2) above, oxygenation of the hemoglobin tends to reverse the reaction, that is, to cause Cl to return to the plasma and CO_2 to escape from the blood.

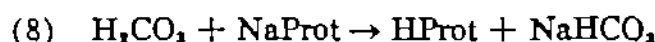


$$(6)\quad KCl + HHb + O_2 \rightarrow KHbO_2 + HCl$$



$$(7)\quad HCl + NaHCO_3 \rightarrow NaCl + H_2O + CO_2$$

Transport by Plasma Protein The plasma proteins are slightly alkaline by reason of combination with sodium A small amount of CO_2 reacts with this Na protein to form sodium bicarbonate and "acidic" protein (HProt)



$$(8)\quad H_2CO_3 + NaProt \rightarrow HProt + NaHCO_3$$

This reaction is reversed in the lungs due to the lower CO_2 tension there, the NaProt is restored and CO_2 is liberated into the alveoli

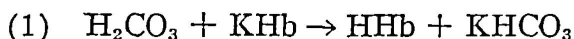
The addition of CO_2 to the blood tends to render the latter more acid. This tendency has to be offset in some manner because the amounts of CO_2 constantly produced in the body are sufficient to induce, if unchecked a degree of acidity incompatible with life. In reaction (8) above there is some buffering of the carbonic acid by the weaker acid, protein This buffering however merely *reduces* the change in hydrogen ion concentration, it cannot nullify it completely There occurs therefore as a result of this reaction a slight but definite increase in the acidity of the blood as it passes through the tissues By far the greater part of the CO_2 carried by the blood, however, is carried by means of the direct and indirect reactions with hemoglobin The fact has been

for the purpose for which the blood passes through the lungs is to become equilibrated with the alveolar air In the administration of volatile anesthetic substances this fact should be kept in mind The anesthetist can control the composition of the alveolar air, but he cannot prevent the latter from having its full effect upon the arterial blood and therefore upon the whole body

The CO_2 pressure relations involved in CO_2 exchanges in the body are indicated in Table IV The volume percentages are added for convenient reference

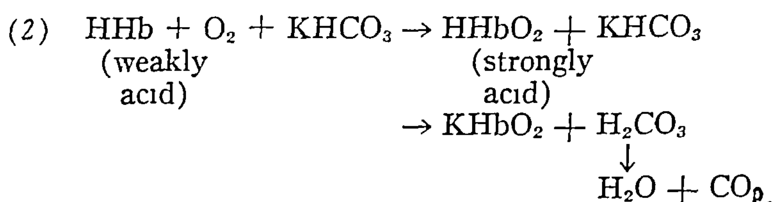
Carbon Dioxide Transport: Each 100 cubic centimeters of arterial blood contains about 53 cubic centimeters of CO_2 of which 3 cubic centimeters are in physical solution and 50 cubic centimeters are in chemical combination All the chemical mechanisms responsible for the transport of CO_2 by the blood are not fully understood, but four are well established and probably account for practically all the CO_2 carried

Direct Hemoglobin Transport Combination with potassium The direct transport of CO_2 by hemoglobin depends upon the ability of CO_2 to diffuse into the red cells Hemoglobin is loosely combined with alkaline radicals in the red cells, chiefly potassium Some of the CO_2 liberated in the tissues, on diffusing directly into the red cells, reacts with this potassium hemoglobinate (KHB) to form potassium bicarbonate and "acidic" (i e, "de-based") hemoglobin



$$(1) \quad H_2CO_3 + KHb \rightarrow HHb + KHCO_3$$

When the blood reaches the lungs the oxygen taken in joins the acidic hemoglobin HHb to form acidic oxyhemoglobin $HHbO_2$ The latter compound is more strongly acid than the unoxygenated HHb and therefore it is able to react with the $KHCO_3$ splitting the latter so as to release CO_2 (which immediately diffuses out of the blood into the alveolar air) and re-form the hemoglobin-potassium combination, this time in the oxygenated state



$$(2) \quad \underset{\text{(weakly acid)}}{HHb} + O_2 + KHCO_3 \rightarrow \underset{\text{(strongly acid)}}{HHbO_2} + KHCO_3 \rightarrow KHbO_2 + H_2CO_3, \quad H_2CO_3 \rightarrow H_2O + CO_2$$

When the $KHbO_2$ returns to the tissues and gives up its oxygen, KHb is again available for a repetition of reaction (1) above

Direct Hemoglobin Transport Combination with amino group Some

TABLE V

CARBON DIOXIDE TRANSPORT

	Tissues	Plasma	Red Cells	Plasma	Lungs	Atmosphere
Isohydric Reactions (Account for the greater amount of CO_2 carried)	I H_2CO_3→	H_2CO_3→	H_2CO_3+KHb ↓			
			HHb+$KHCO_3$ (+O_2) ↓	←O_2	←O_2	←O_2
			$HHbO_2$+$KHCO_3$ ↓			
			$KHbO_2$ + H_2CO_3→	H_2CO_3→	H_2O + CO_2→	CO_2
	II H_2CO_3→	H_2CO →	H_2CO_3+HbNH ↓			
			HbNHCOOH+H_2O (+O_2) ↓	←O_2	←O_2	←O_2
			$NbO_2NHCOOH$+H_2O ↓			
			HbO_2NH + H_2CO_3→	H_2CO_3→	H_2O + CO_2→	CO_2
	III. H_2CO_3→	H_2CO +NaCl ↓				
		$NaHCO_3$+HCl→	HCl+KHb ↓	←O_2)	←O_2	←O_2
			KCl+HHb (+O_2) ↓			
			$HHbO_2$+KCl ↓			
			$KHbO_2$ + HCl→	HCl+$NaHCO_3$ ↓		
				NaCl+H_2CO_3→	H_2O + CO_2→	CO_2
Buffering Reaction (Involves some increase in hydrogen ion concentration)	IV H_2CO_3→	H_2CO_3 + NaProt→	$NaHCO_3$+HProt→	NaProt + H_2CO_3→	H_2O + CO_2→	CO_2

It should be noted that reactions (I) and (II) representing direct transport by hemoglobin, depend pon the diffusibility of CO into the interior of the cell across the cell membrane and that reaction (III) representing indirect transport by hemoglobin, depends upon the non-diffusibility of N and K across the cell membrane.

most common for it complicates many clinical conditions, both medical and surgical There are four types of anoxia, according to the cause producing the condition

Types of Anoxia *Anoxic Anoxia* Anoxic anoxia is a condition of diminished oxygen tension in the arterial blood It always involves deficient saturation of the hemoglobin with oxygen It may be caused by (a) an inadequate amount of oxygen in the atmosphere, (b) defective

mentioned above that oxygenation of the hemoglobin in the lungs renders it more strongly acid, thereby assisting in the unloading of CO_2 (reactions (2) and (6)) The reverse reaction in the tissues, that is, the change of HbO_2 to Hb, represents a corresponding decrease in acidity This decrease in acidity due to release of oxygen from hemoglobin almost entirely offsets the increase in hydrogen ion concentration which the passage of CO_2 from the tissues into the blood would otherwise produce The quantitative importance of this mechanism is considerable The change of hemoglobin from the oxygenated to the reduced state permits the blood to accommodate a very large amount of CO_2 without any change whatever in hydrogen ion concentration, hence the transport of CO_2 by means of the direct and indirect reactions with hemoglobin is said to be "isohydric"

In the first two of these isohydric reactions the carbonic acid goes itself into the red cells to react with the hemoglobin, whereas in the third the carbonic acid reacts with alkali which is near-at-hand in the plasma, thus freeing another acid radical, Cl, which it sends as its emissary into the red cells to react with the hemoglobin The net result with reference to hydrogen ion concentration is the same In connection with the third (indirect) reaction it is obvious that on the addition of CO_2 to the blood, Cl is transferred from the plasma to the interior of the red cells For this reason the term "chloride shift" has been applied to the reaction This migration of chloride is easily proved by separating the cells from the plasma before the addition of CO_2 to the blood and measuring separately the chloride content of the cells and of the plasma, and then measuring the chloride content of cells and plasma separated after CO_2 has been added to the blood

The reaction



$$CO_2 + H_2O \rightarrow H_2CO_3$$

proceeds very slowly in watery solutions such as plasma In the red cells has been found an enzyme, carbonic anhydrase, which tremendously speeds up the reaction in either direction, that is, causes equilibrium to be attained in a very much shorter time

The reactions responsible for the transport of CO_2 described above are summarized diagrammatically in Table V

ANOXIA

Anoxia means a deficient supply of oxygen to the tissues The term anoxemia, as commonly used, has the same meaning, though literally it signifies a lack of oxygen in the blood

Anoxia is the gravest of the "deficiency diseases," and perhaps the

esses of the cells are disturbed by the diminished tension under which oxygen is supplied Body cells in general are sensitive with regard to the pressure under which their oxygen is available, and the cells of the central nervous system, including the medullary centers, are particularly sensitive to any decrease of oxygen tension In anoxic anoxia, in addition to the decreased tension, the amount of oxygen available to the body is reduced also, this is an added impediment to the oxidative processes A third and less direct disadvantage of anoxic anoxia is not present in the other types This is the excessive elimination of carbon dioxide which occurs The low oxygen tension acts as an effective stimulus of the respiratory center, the resultant increased breathing augments the intake of oxygen, which is its purpose, but also it incidentally speeds the elimination of CO_2 This is a disadvantage because CO_2 in suitable concentration serves as a catalyst for the chemical reaction by which oxygen is liberated from hemoglobin in the tissues When the CO_2 tension in the body is decreased the dissociation of oxyhemoglobin is impaired and therefore a certain amount of oxygen in the blood is rendered unavailable to the tissues

Anemic Anoxia Anemic anoxia is anoxia due to a decreased amount of functioning hemoglobin in the blood The chief causes are acute and chronic anemias of all types, and poisoning by substances which combine with hemoglobin such as carbon monoxide, nitrites and chlorates Carbon monoxide deviates hemoglobin from its oxygen-carrying function by forming a stable combination with it

The ill effects of anemic anoxia are not as severe as those of the anoxic type, chiefly because in the former the tension of whatever oxygen the blood does contain is normal, for the blood, though deficient in hemoglobin, is fully exposed to normally ventilated alveoli Even if blood plasma free of red cells were to circulate through the lungs it would acquire oxygen under the normal tension, in spite of the fact that the amount going into solution would be very small The tension of any gas in solution or in an easily dissociable combination (e g oxyhemoglobin) is equal to the pressure of that gas in the surrounding atmosphere In the case of the blood the only gaseous atmosphere with which it comes in contact is the alveolar air The oxygen tension in the arterial blood therefore depends only on the tension in the alveolar air and on how closely the blood is exposed to the latter Anemic anoxia causes no appreciable stimulation of breathing, indeed, nothing is to be accomplished by increased respiration, since normal arterial oxygen tension, which may be considered the "goal of breathing" is already present

'Air hunger' is described as a frequent symptom of the [illegible]

transfer of oxygen from the atmosphere to the alveoli of the lungs or, (c) impaired transfer of oxygen from the lumen of the alveoli to the pulmonary blood

(a) *Deficiency of oxygen* in the general atmosphere occurs only at high altitudes, where it is responsible for mountain sickness In surgery a similar deficiency occurs often in connection with inhalation anesthesia, when an anesthetic gas such as nitrous oxide is given in such high concentration that an insufficient proportion of oxygen is available to the patient Moreover oxygen is rapidly consumed and carbon dioxide replaces it in the gas mixture and unless a constant supply of additional oxygen is made available and carbon dioxide removed to make room for it, a dangerous degree of anoxia may result

(b) *The transfer of oxygen from the atmosphere to the alveoli of the lungs* is impeded in all conditions of deficient pulmonary ventilation, of which there are two groups, namely, conditions in which the air passages are obstructed at some level, whether by occlusion from within their lumen or by compression from without, and conditions in which the respiratory movements are decreased, that is, the renewal of the alveolar air is slower than normally

Examples of the "obstructive" type of deficient ventilation are, from within, a foreign body occluding the trachea, a mucous plug occluding a bronchus as in massive collapse, and pneumonic exudate or edema fluid filling the alveoli themselves, and from without, air, blood or pus in the pleural space

The "paralytic" type of deficient ventilation may be central or peripheral in origin, and depend upon nervous or chemical factors A few examples may be mentioned Depression of the respiratory medullary center by morphine, ether, or other toxins, involvement of the spinal motor nerve cells by poliomyelitis or novocaine anesthesia, shallow breathing induced reflexly by the pain in pleurisy or pneumonia, alkalemia from persistent vomiting diminishing the excitability of the respiratory center The common factor in all these instances, both obstructive and paralytic is a decreased volume of air ventilating the alveoli per minute

(c) *There is impaired transfer of alveolar oxygen across the alveolar wall* when the latter is thickened or its permeability is diminished, as in emphysema, and in moderate degrees of pneumonitis or edema when the alveolar wall is swollen but the alveolar lumen is not completely filled with exudate or fluid Patent foramen ovale and other congenital anomalies which permit shunting of some of the blood away from exposure to the alveolar air belong to this group

Anoxic anoxia is harmful primarily because in it the oxidative proc-

of interest In the anoxic type, the decreased oxygen tension becomes the determining factor in respiration, and induces hyperpnea which, while it combats the oxygen lack, is a state of overventilation as far as carbon dioxide is concerned The result is excessive elimination of CO_2 and consequently a diminished concentration of CO_2 in the tissues This is a disadvantage since, as mentioned above, CO_2 acts to facilitate the dissociation of oxyhemoglobin In anemic anoxia the rate of elimination of CO_2 is practically normal it is not accelerated because there is little or no hyperpnea it is not retarded because the blood circulates more rapidly to compensate for the deficiency in carrying capacity, and this incidentally assists in the portage of CO_2, which is not as rigidly dependent upon hemoglobin as oxygen carriage In stagnant anoxia removal of carbon dioxide is retarded because of the slow blood flow Hence CO_2 concentration in the tissues is higher than normal This is advantageous in that it aids the liberation of oxygen from the capillary blood to the tissues

Histotoxic Anoxia Histotoxic anoxia is inability of the tissue cells to utilize oxygen brought to them by reason of a disorder of the oxidative chemical machinery within the cells Cyanide poisoning is an example

Effects of Anoxia *Factors Determining Symptoms of Anoxia* The symptoms produced by general anoxia vary according to the suddenness with which the condition develops its degree and its duration They vary also to some extent with the type of anoxia, depending chiefly on whether or not the tension of oxygen in the arterial blood is altered, and on disturbances of CO_2 elimination The varied and often confusing symptomatology of anoxia is explained further by the fact that in each clinical instance of the condition there are symptoms due to associated factors and not to the anoxia itself For example, anoxia in connection with general anesthesia may be complicated by the specific effects of the agent used and of the premedication, and by symptoms dependent directly on the pathological conditions present or the operative procedure itself Anoxia in a case of massive hemorrhage is complicated by symptoms referable to the low blood pressure brought on by the sudden reduction of circulating blood volume If the latter is restored to normal by infusion of saline solution the blood pressure is raised considerably and the symptoms dependent on low blood pressure are largely relieved whereas the state of anoxia still persists In pneumonia anoxia is responsible for symptoms to some extent but the general poisoning by bacterial toxins affecting various organs and tissues plays probably a greater part.

anoxia resulting from massive hemorrhage This at first seems to contradict the above statement that respiratory stimulation does not occur in this type of anoxia, because the arterial oxygen tension remains normal When increased respiratory efforts occur after hemorrhage they are related to the fall in blood pressure caused by sudden loss of blood volume rather than to any chemical alteration of the blood Sudden lowering of blood pressure from any cause stimulates the sensory nerve ending of the carotid sinus causing afferent impulses to ascend to the cardiovascular centers and stimulate them These same impulses extend to the respiratory center and stimulate it to increased activity

Each 100 cubic centimeters of normal arterial blood contains about 20 cubic centimeters of oxygen However only about 5 cubic centimeters of the latter is used in the passage of the blood through the tissues during rest When the hemoglobin is reduced as low as 50 per cent, 100 cubic centimeters of blood are still able to carry 10 cubic centimeters of oxygen, which is ample to supply the needs (5 cubic centimeters) of the body at rest Moreover any deficiency can be readily made up by a more rapid rate of circulation of the blood During activity the latter compensation for the anemia is quickly overreached and respiratory distress, rather than effective stimulation, occurs

Stagnant Anoxia Stagnant anoxia is anoxia due to a deficient amount of blood circulating per minute It is caused primarily by circulatory failure rather than respiratory failure It may be general or local Examples of the former are heart failure, and widespread failure of the blood vessels, whether of the arterioles, as in vasomotor paralysis due to spinal anesthesia, or of the capillaries, as in surgical shock Local stagnant anoxia may be arterial or venous in origin, since a diminished blood-flow results when either the afferent or efferent vessel of a region is partially or completely blocked The obstruction may be organic as in arterial or venous thrombosis, or spastic as in Raynaud's disease Local stagnant anoxia due to capillary disturbance does occur, as in the blue color of the lips resulting from exposure to cold but this variety is seldom of surgical interest

In stagnant anoxia the oxygen tension of the arterial blood is normal, just as in the anemic type The oxygen content of the arterial blood is normal also Carbon dioxide tends to accumulate in the tissues, and this aids in the ready release of the oxygen from the blood, since acids in general, and especially CO_2, accelerate the dissociation of oxyhemoglobin The slow rate of flow through the tissues is an additional factor which favors efficient utilization of whatever oxygen is available

The relation of CO_2 to the three types of anoxia mentioned above is

of interest In the anoxic type, the decreased oxygen tension becomes the determining factor in respiration, and induces hyperpnea which, while it combats the oxygen lack, is a state of overventilation as far as carbon dioxide is concerned The result is excessive elimination of CO_2 and consequently a diminished concentration of CO_2 in the tissues This is a disadvantage since, as mentioned above, CO_2 acts to facilitate the dissociation of oxyhemoglobin In anemic anoxia the rate of elimination of CO_2 is practically normal it is not accelerated because there is little or no hyperpnea, it is not retarded because the blood circulates more rapidly to compensate for the deficiency in carrying capacity, and this incidentally assists in the portage of CO_2, which is not as rigidly dependent upon hemoglobin as oxygen carriage In stagnant anoxia removal of carbon dioxide is retarded because of the slow blood flow Hence CO_2 concentration in the tissues is higher than normal This is advantageous in that it aids the liberation of oxygen from the capillary blood to the tissues

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Effects of Anoxia *Factors Determining Symptoms of Anoxia* The symptoms produced by general anoxia vary according to the suddenness with which the condition develops, its degree and its duration They vary also to some extent with the type of anoxia, depending chiefly on whether or not the tension of oxygen in the arterial blood is altered, and on disturbances of CO_2 elimination The varied and often confusing symptomatology of anoxia is explained further by the fact that in each clinical instance of the condition there are symptoms due to associated factors and not to the anoxia itself For example, anoxia in connection with general anesthesia may be complicated by the specific effects of the agent used and of the premedication, and by symptoms dependent directly on the pathological conditions present or the operative procedure itself Anoxia in a case of massive hemorrhage is complicated by symptoms referable to the low blood pressure brought on by the sudden reduction of circulating blood volume If the latter is restored to normal by infusion of saline solution the blood pressure is raised considerably and the symptoms dependent on low blood pressure are largely relieved whereas the state of anoxia still persists In pneumonia anoxia is responsible for symptoms to some extent but the general poisoning by bacterial toxins affecting various organs and tissues plays probably a greater part.

Effects of Anoxia on Respiratory System Respiration is stimulated by moderate degrees of anoxia, especially the anoxic type, as mentioned above In any case the response to anoxia is not as great as that to stimulation by CO_2 excess, for oxygen lack is not the normal stimulus It does not increase the depth of breathing as effectively as CO_2 excess, and it constantly tends to counteract its own stimulating effect by causing too rapid removal of CO_2 and consequent alkalemia That anoxia is an abnormal type of respiratory stimulus is sometimes evidenced by an abnormal type of response For example, in severe hemorrhage (ruptured ectopic gestation) the respiratory response may take the form of violent and repeated yawning This however may be partly dependent on fall of blood pressure

Severe oxygen lack depresses and ultimately paralyzes the respiratory center Indeed the so-called stimulation by moderate anoxia might perhaps be considered rather an irritation and merely a stage in the respiratory depression which is the proper effect of the condition The respiratory center deprived of oxygen may be compared to a fish out of water Though the fish at first appears "stimulated" and exhibits vigorous activity, it cannot really be considered "stimulated" in a beneficial sense, it is a dying fish from the moment it is taken out of the water The increase or "stimulation" of breathing in anoxia may likewise be considered a very early symptom of a dying respiratory center

Under all normal and usual conditions, whenever the tissues suffer oxygen deficiency there is present also a CO_2 excess If under abnormal conditions the association of these two factors is still maintained, the response on the part of the respiration is more efficient than it is if the factors are dissociated to more or less degree

Effects on Nervous System The nervous system, particularly its higher portions, is very sensitive to oxygen lack Symptoms referable to it are disturbances of consciousness, intelligence, judgment and motor coordination, convulsions or paralyses may occur

Effects on Other Systems Circulatory symptoms of certain stages of anoxia are cyanosis and increase of blood pressure and pulse rate One of the compensatory reactions to anoxia is increase of the number of red cells and concentration of hemoglobin Ultimately the circulation suffers collapse As direct noxious effects of general anoxia or as compensatory reactions to it, there may occur symptoms referable to the gastro-intestinal tract, such as nausea, vomiting and diarrhea, to the musculoskeletal system, such as weakness, to the kidney and to all the other organs

CYANOSIS

Definition Cyanosis is a bluish color of the tissues due to an increased absolute amount of unoxygenated hemoglobin in the capillary blood There is normally a considerable amount of unoxygenated hemoglobin in the veins, producing the bluish color of the latter, but cyanosis is not present unless there is a similar large amount of unoxygenated hemoglobin in the smaller vessels, particularly the capillaries Possibly the state of the blood in the arterioles and venules is also an appreciable contributing factor

The term "absolute amount" signifies that a certain definite quantity of hemoglobin per hundred cubic centimeters of blood must be present in the unoxygenated state for the presence of cyanosis, regardless of whether this reduced hemoglobin is a large or small fraction of the total hemoglobin content of the blood In very marked anemia nearly all the hemoglobin in the blood of the capillaries must be unoxygenated for the production of cyanosis In polycythemia, on the contrary, with the total hemoglobin at a high level, only a small fraction of the total need be in the reduced state to produce cyanosis, the presence of a large oxygenated fraction has no appreciable bearing on the cyanosis

Pathogenesis and Types of Cyanosis Each 100 cubic centimeters of blood contains approximately 15 grams of hemoglobin and is capable of carrying about 20 cubic centimeters of oxygen A minimum of 5 grams of unoxygenated hemoglobin per 100 cubic centimeters of capillary blood is required to produce visible cyanosis Ordinarily the *arterial blood* leaves the heart almost fully saturated, that is, containing roughly about 19 cubic centimeters of oxygen per 100 cubic centimeters of blood This blood is bright red *Venous blood* normally contains approximately 14 cubic centimeters of oxygen per 100 cubic centimeters, for only a relatively small fraction of the available blood oxygen is consumed in the tissues under resting conditions This normal venous blood is red too, for it still contains a large amount of the oxyhemoglobin of the arterial blood but it is a very dusky red, due to the hemoglobin whose oxygen has been given up in the tissues The statement that venous blood is dusky red instead of blue might seem to contradict common observation, for the superficial veins, for example, those of the dorsum of the hand, are obviously bluish in color These vessels however carry blood from only one portion of the body, in regions which are less active or more vascular, the venous blood is correspondingly more red in color The mixed venous blood from all parts of the body has an intermediate dusky red color

The oxygen content of *capillary blood* is about midway between that of arterial (20 cubic centimeters) and venous (15 cubic centimeters) blood, therefore its actual content of 17 5 cubic centimeters is 2 5 cubic centimeters short of saturation (2 5 volumes per cent unsaturation) The 15 grams Hb in each 100 cubic centimeters of capillary blood, though capable of holding 20 cubic centimeters oxygen, is therefore partly oxygenated and partly unoxygenated, in the ratio of 17 5 2 5 Hence the unoxygenated portion of the hemoglobin in capillary blood amounts to about 2 1 grams under normal conditions As stated above, cyanosis does not appear unless the reduced Hb amounts to approximately 5 grams per 100 cubic centimeters of capillary blood Since the amount of oxygen in the capillaries is an average of the amount in the arteries and veins, marked unsaturation of the capillary blood may occur as the result of (1) deficient oxygenation of the arterial blood, as for example in respiratory obstruction, or (2) abnormally increased utilization in the tissues of the arterial oxygen, the latter being at the normal level but the venous blood having a diminished oxygen content, as for example, in slowing of the circulation from cardiac failure

These two types of cyanosis, respiratory and circulatory, may be illustrated by the following approximate figures

TABLE VI

RELATIVE AMOUNTS OF OXYGENATED AND UNOXYGENATED HEMOGLOBIN IN THE BLOOD IN TWO TYPES OF CYANOSIS

		Arterial Blood	*Mixed Venous Blood*	*Capillary Blood (Average of Arterial and Venous)*
Normal	Grams HbO_2	14	11	12 5
	Grams Hb	1	4	2 5—No cyanosis
Respiratory Cyanosis	Grams HbO_2	11	8	9 5
	Grams Hb	4	7	5 5—Cyanosis
Circulatory Cyanosis	Grams HbO_2	14	5	9 5
	Grams Hb	1	10	5 5—Cyanosis

Relation Between Cyanosis and Anoxia The causes of cyanosis are in general similar to those of anoxia but cyanosis is not always an accurate index of the severity of the anoxia present As an exaggerated example, in marked anemia the total hemoglobin may be only 30 per cent of normal, corresponding to less than 5 grams per 100 cubic centimeters of blood In such a case cyanosis would not appear even though

anoxia were so severe that all the Hb were in the reduced state, for a minimum of 5 grams of unoxygenated hemoglobin is required to produce visible cyanosis Peripheral vasconstriction may prevent cyanosis by reducing the amount of blood in the surface vessels, even though a marked degree of anoxia is present. It is evident from these examples that a patient may be suffering from severe oxygen want without manifesting cyanosis

The reverse, namely the presence of cyanosis in the absence of marked anoxia, does occur, but is less frequent and therapeutically less important An example of chronic cyanosis of this kind is found in polycythemia of any type Temporary cyanosis often results from exposure to cold and dampness, due to a stagnant condition of the blood in the surface capillaries permitting excessive reduction of the oxyhemoglobin It does not indicate a corresponding degree of anoxia in the deeper tissues or in the body as a whole

The carbon dioxide content of the blood has no bearing upon cyanosis There is no relation whatever between CO_2 retention and cyanosis In depression of the respiratory center cyanosis develops solely because of inadequate oxygenation of the hemoglobin of the blood It is true that as a rule carbon dioxide accumulates at the same time but the two events oxygen deprivation and carbon dioxide excess, are not rigidly related to each other Often it is even advisable to administer additional CO_2 for the purpose of stimulating the respiratory center in such a case, and the presence or absence of cyanosis should have no influence in deciding this matter Yet it sometimes happens that the surgeon will request the anesthetist not to administer CO_2 to a patient who has stopped breathing, perhaps with the observation that the patient is "blue enough already" There is obviously a limit to the amount of CO_2 which can accumulate in the body when breathing has ceased A moment's reflection upon the chemical formula of carbon dioxide makes this clear CO_2 cannot be formed without oxygen It is to be expected therefore that many patients who are cyanotic from depression of the respiratory center are in need of the stimulating action of the normal respiratory hormone

Asphyxia Three conditions referable to the respiratory system whose interrelations should be noted are anoxia, cyanosis and dyspnea (labored breathing) There is a tendency to assume that these are constantly associated, because of the fact that all three are present in ordinary asphyxia Asphyxia is a condition in which there is not only a deficient oxygen supply but also an excessive accumulation of CO_2 The most familiar normal example is strenuous muscle exertion The simplest

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TABLE VII

SUMMARY OUTLINE OF RESPIRATORY SYSTEM

FUNCTIONS

1 O_2 Supply and CO_2 Removal
2. Acid—Base Regulation
3 Temperature Regulation
4 Water Excretion

MECHANICS

- Air Pressures mm. Hg
  - Resting −5
  - Inspiration −10
  - Expiration +5
  - Forced Breathing 70 to 100
- Air Volumes cc.
  - Complemental 1500 } Vital Capacity 3500
  - Tidal {Alveolar 350, Dead Space 150} 500 } Index of respiratory reserve
  - Supplemental 1500 }
  - Residual 1500 { Buffer for {Temperature, Chemical Composition}

CONTROL

- I Nervous (Mainly rate and rhythm)
  - Efferents
    - Phrenic
    - Intercostals
  - Center
    - Medulla
      - Bilateral
      - Automatic
      - Reflex
    - Cord—Subordinate
  - Afferent
    - Respiratory Organs
      - Vagus
      - Proprioceptors
    - Everywhere
      - Cerebrum
        - Cortex Volition
        - Thalamus Emotion
      - N V Sneeze
      - N.IX Swallow
      - N.X. Cough
      - Sphincter ani etc.
- II. Chemical (Mainly depth and ventilation)
  - H ion Concentration in Center (Gesell)
    1 CO_2 Great diffusibility into center
    2 H ion Concentration of blood
    3 O_2 lack Incomplete oxidation in center
  - Drugs
    - Caffeine
    - Morphine
- III. Apnea

CHEMISTRY

- Oxygen Exchange
- CO_2 Exchange
- Anoxia
- Cyanosis

instance of abnormal asphyxia is complete obstruction of the respiratory passages In both these cases a marked degree of all three factors develops, namely oxygen want, cyanosis and increased respiratory efforts Under certain conditions, however, any one factor may occur without the others. (1) As mentioned above, anoxia without cyanosis may occur in anemia, or in the presence of peripheral vasconstriction In most cases of anemia there is also absence of noticeable dyspnea at least during rest This may be explained by the lack of any CO_2 excess and by the normal tension under which the reduced amount of oxygen exists in the blood (2) Cyanosis without either anoxia or dyspnea occurs in polycythemia, due to the abundance of hemoglobin available, a large enough fraction of it may remain permanently unoxygenated to produce cyanosis, while the remainder is adequate to supply the oxygen needs of the body (3) A familiar example of dyspnea without anoxia or cyanosis occurs in the acidosis of diabetes or uremia In these conditions there is no disturbance of the oxygenation of the blood, hence the absence of anoxia and cyanosis The dyspnea is related to one of the non-oxidative functions of the respiratory system, namely the regulation of acid-base balance The purpose of the overbreathing is to eliminate larger amounts of the acid substance CO_2 in order to offset the abnormal accumulation of other acid substances. In an analogous manner, increased respiratory effort is sometimes related to the need for temperature regulation or water elimination, in which case it is unassociated with anoxia or cyanosis

Sulfanilamide Cyanosis Cyanosis of varying degree is observed in a large percentage of patients undergoing intensive treatment with sulfanilamide This cyanosis, formerly attributed entirely to the presence of methemoglobin or sulfhemoglobin, has been shown by Marshall and Walzl to be unaccompanied by any decrease in the oxygen carrying capacity of the blood and to occur in some cases without any non-functional iron-pigment being present in the blood Small amounts of methemoglobin were found in some cases, but this substance was not believed to be the principal cause of the cyanosis These authors suggest that in sulfanilamide cyanosis the dark color of the blood may be due to the presence of a black oxidation product of the drug which stains the red blood cells

Ottenberg and Fox found that dilute solutions of sulfanilamide on very brief exposure to ultraviolet light develop a strong violet color. The nature of this chemical change is unknown It was found that when red cells are added to such solutions they at once adsorb the violet substance and assume the color shown by the red cells of patients receiving sulfanilamide. Plasma added to the violet solutions causes the color to dis-

appear Wendel, *et al*, though confirming these findings of Ottenberg and Fox, on the basis of spectrophotometric and gasometric studies of the blood of patients with sulfanilamide cyanosis believe that the abnormal color is for the most part due to methemoglobin

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  - Inspiration −10
  - Expiration +5
  - Forced Breathing 70 to 100
- Air Volumes cc.
  - Complemental 1500
  - Tidal 500 (Alveolar 350; Dead Space 150)
  - Supplemental 1500
    - (Complemental, Tidal, Supplemental:) Vital Capacity 3500; Index of respiratory reserve
  - Residual 1500 — Buffer for Temperature; Chemical Composition

CONTROL

- I Nervous (Mainly rate and rhythm)
  - Efferents
    - Phrenic
    - Intercostals
  - Center
    - Medulla
      - Bilateral
      - Automatic
      - Reflex
    - Cord—Subordinate
  - Afferent
    - Respiratory Organs
      - Vagus
      - Proprioceptors
    - Everywhere
      - Cerebrum
        - Cortex Volition
        - Thalamus Emotion
      - N V Sneeze
      - N.IX Swallow
      - N.X Cough
      - Sphincter ani etc.
- II. Chemical (Mainly depth and ventilation)
  - H ion Concentration in Center (Gesell)
    1. CO_2 Great diffusibility into center
    2. H ion Concentration of blood
    3. O_2 lack Incomplete oxidation in center
  - Drugs
    - Caffeine
    - Morphine
- III Apnea

CHEMISTRY

- Oxygen Exchange
- CO_2 Exchange
- Anoxia
- Cyanosis

REGULATION OF BODY TEMPERATURE

During health the surface temperature varies considerably in different parts of the body If it becomes uniform throughout the body discomfort results Factors which influence body surface temperature in health are

External Factors	Temperature Humidity Wind Clothing	Internal Factors	Basal Metabolic Rate Muscular Work Surface Blood Supply

These factors act by influencing heat production or heat loss, the balance between which determines the temperature Heat production occurs mainly in the skeletal muscles as the result of oxidative processes, a certain amount of heat is also produced in gland tissue and in the other tissues Heat loss occurs chiefly by conduction and radiation from the surface (75 per cent) and by evaporation from the skin and lungs (25 per cent) The amount of heat lost in the excreta is negligible

NERVOUS CONTROL OF BODY TEMPERATURE

As with most physiological constants, body temperature is maintained partly by nervous mechanisms and partly by chemical mechanisms The nervous control of body temperature is essentially reflex in nature, that is, it involves all the elements of a reflex arc

1 The *adequate stimulus* is any change in the temperature of the body surface or of the blood Such a change may result from any of the external or internal factors listed above

2 The *receptors* are the temperature sense organs in the skin The heat center in the brain may also be considered a receptor in a sense, in that it may be directly stimulated by any change in the temperature of the blood bathing it

3 The *afferent pathways* are the temperature sensory fibers in the peripheral nerves and in the white columns of the spinal cord

4 The *centers* are partly spinal but chiefly cerebral

Spinal Center The afferent temperature impulses due to cold may affect anterior horn motor cells so as to cause greater activity in skeletal remains intact, caudally placed lesions cause a disturbance of regulation muscle (shivering) thus increasing heat production, and also affect cells of vasomotor fibers so as to cause vasoconstriction at the surface of the body and thus diminish heat loss Heat may produce the reverse effects

Cerebral Center. The cerebral center situated in the hypothalamic

region is the more important, for its influence extends throughout the body because it is connected with the whole system of afferent and efferent fibers, and it predominates over the activities of the spinal temperature reflexes Ranson's observations on cats and monkeys indicate that the temperature regulating functions of the hypothalamus are more or less segregated anterioposteriorly Anteriorly placed lesions are likely to impair regulation against heat while regulation against cold in both directions

5 The *efferent pathways* are

(a) Vasomotor fibers

(b) Sweat gland fibers

(c) Motor fibers to skeletal muscles and to gland tissue

(d) Fibers from the heat center to the respiratory center and cardio-vascular centers

6 The *effector organs* are the blood vessels of the skin, the sweat glands, the skeletal muscles, the lungs and the cardio-vascular system

CHEMICAL CONTROL OF BODY TEMPERATURE

The chemical means of regulating body temperature are not as well understood as the nervous mechanisms just mentioned The secretion of the thyroid gland increases heat production by its effect on metabolism It is probable that exposure to external cold reflexly stimulates the thyroid gland so as to increase its secretion and thus set in action this chemical factor Adrenalin tends to raise the temperature both by stimulating metabolic processes to some extent and also by diminishing heat loss by inducing vasoconstriction

Under the action of a general anesthetic temperature regulation is impaired to greater or less degree because of the depressing effect upon the controlling cerebral center, and probably in part also because of the effect upon the spinal and other peripheral nerve pathways When a limb is completely denervated the temperature of the part becomes elevated for a few days, because of loss of the partial vasoconstriction normally present, thereafter the part becomes colder than normal because the blood vessels develop an independent tonicity, and also because there is some impairment of heat production and of circulation due to the lack of muscular activity

In high spinal cord injuries there is marked interference with temperature regulation due to impaired nervous control of the skeletal muscles (heat production) and of the blood vessels and sweat glands of the skin (heat loss)

PHYSICAL FACTORS IN REGULATION OF BODY TEMPERATURE

It is common experience that dampness makes hot weather more disagreeable, and also makes cold weather more disagreeable. This seeming paradox is explained by the contrary effects which moisture has upon the different methods by which heat is lost from the surface of the body Normally radiation and conduction together account for about 75 per cent of the heat loss and evaporation for the remaining 25 per cent, as mentioned above, but this proportion holds only for ordinary room temperatures It is apparent that when the room temperature is at or above body temperature the usual heat gradient is abolished or reversed and there can not possibly be any conduction or radiation of heat away from the body Evaporation then becomes the sole means of heat loss, the relative values becoming

Conduction and radiation, 0 per cent,
Evaporation, 100 per cent

If the air is dry, evaporation of water from the surface of the body occurs readily, and the consequent rapid dissipation of heat renders the high room temperature more tolerable If however the air is moist, it is obvious that evaporation, the sole compensatory mechanism at the time, will be retarded and the high room temperature is more disagreeable

When the room temperature is lower than usual, the temperature gradient between body and room is steeper with the result that conduction and radiation of heat away from the body are accelerated, whereas evaporation is diminished Evaporation may in fact become negligible, at low temperatures, the relative values becoming

TABLE VIII

INFLUENCE OF ENVIRONMENT ON BODY TEMPERATURE REGULATION

1 *Environment*	2 *Predominant Means of Heat Loss*	3 *Effect on 2 of High Humidity*	4 *Subjective Result*	5 *Effect on 2 of Low Humidity*	6 *Subjective Result*
Hot Weather	Evaporation	Decreases	Heat aggravated	Increases	Heat tolerated better
Cold Weather	Conduction	Increases	Cold aggravated	Decreases	Cold tolerated better

Conduction and Radiation, 100 per cent,

Evaporation, 0 per cent

The heat capacity of water vapor is greater than that of air. Therefore if there is much moisture in the air at the low room temperature, loss of heat from the body is accelerated and the cold is more disagreeable than it would be if the air were dry and less able to carry away heat.

To summarize briefly: At high temperature *Evaporation* is the chief means of heat loss and is *impeded by moisture* in the air, at low temperatures *Radiation and Conduction* are the chief means of heat loss and are *augmented by moisture* in the air.

FEVER

During a fever the same mechanisms control the body temperature as in health, but the level at which the system is set is higher than normal, and the regulation is somewhat less sensitive. The initial rise of temperature above normal is brought about chiefly by curtailment of heat loss. When fever is established there is increased heat production, and also, when the fever becomes stationary, a corresponding increased rate of heat loss. It is obvious that even at the elevated body temperature the balance between heat prodution and heat loss must still be maintained at all times except when the temperature is actually rising or falling. Fever is not in itself dangerous, even though persisting a long time and at a high level, e.g., 104° F. Acidosis is not constantly present in fever. Antibody formation takes place more rapidly during fever than at normal body temperature.

Causes of fever are:

1. The action of certain proteins and products of protein decomposition on the heat center. Fever associated with hemorrhage seems to be dependent mainly on disintegration of blood platelets.

2. Dehydration, interfering with heat loss.

3. Brain lesions, affecting the heat center.

Chill. In a chill, the subjective sensation of the patient is dependent entirely on the temperature of the *surface* of the body. This explains the seeming paradox of high body temperature existing at the time of a chill. The patient has no direct knowledge of the temperature of the *interior* of his body, since that region is not provided with nerves of temperature sense. It is a familiar fact that internal organs may be burned by cautery at operation without any sensation of heat being appreciated by the conscious patient. A chill occurs as part of the mechanism of raising the body temperature above normal. The exciting factor, such as infecting organisms or foreign protein substances, acts upon the heat center. The latter, for the purpose of retaining body heat

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induces widespread vasoconstriction at the surface of the body This reduces the temperature of the skin, and therefore diminishes the rate of heat loss to the environment, so that the temperature within the body begins to rise The patient, however, is only aware of the fall of temperature at the periphery, where there are sensory endings capable of appreciating it, but is unaware of the consequent increased warmth of the deeper tissues Shivering and other reactions occur in response to the cold skin just as if the coldness had been induced by the external environment The application of heat to the body artificially besides giving comfort to the patient favors the purpose of the chill of raising body temperature quickly Once the blood has attained a certain temperature it acts upon the heat center so as to inhibit further measures to conserve heat The peripheral vasoconstriction then relaxes, the skin receives a free supply of warm blood and the chill ceases

The normal temperatures for 52 points on the body surface have been determined by Eddy and Taylor They found the following approximate average values base of great toe, 29 2° C , knee, 32° C , trunk, 32 5 to 33 5° C , elbow, 33 5°, hand 33° C However there were variations in different individuals of as much as 4 to 6 degrees, hence the range of normal surface temperature values is quite wide

Chapter VIII

THE SALIVARY GLANDS

Efferent Nervous Control The salivary glands are apparently subject to nervous control exclusively, no hormone control having been discovered. A possible hormonic influence, however, has been suggested by Weinberger in connection with the hypersalivation occasionally observed in menstruation, pregnancy, and the menopause

The secretory nerves belong to the autonomic system and, as usual, are of two types, cranial autonomic and thoraco-lumbar sympathetic. However, there is not the customary mutual antagonism between the effects produced by these two nerve supplies Whereas double autonomic innervation often consists of a purely motor and a purely inhibitory supply, in the case of the salivary glands both nerve supplies are motor in that their activity causes the glands to secrete, but the secretion differs in amount and in quality in the two cases In the dog stimulation of the cranial (parasympathetic) innervation induces the secretion of a large amount of thin watery saliva, whereas stimulation of the sympathetic nerve supply causes the secretion of a very scanty amount of thick viscid saliva. One can remember that the scanty thick saliva results from sympathetic stimulation by recalling that all the vasoconstrictor nerves belong to the sympathetic system, and vasoconstriction, occurring simultaneously with secretory activity of the gland cells would naturally limit the volume and decrease the fluidity of the saliva produced

In cases of parotid salivary fistula it is sometimes desirable to sever the parasympathetic nerve supply of the gland at the most accessible part of its course, i e, at the auriculotemporal nerve, in order to check the secretion of saliva

Afferent Nervous Control Various types of stimuli can induce secretion of saliva The afferent side of the nervous control of salivation can be followed by tracing the pathways of afferent impulses from the receptor end-organs to the salivary nuclei in the medulla

The most important normal stimulus is the taste of food the afferent taste impulses travel to the medulla via the lingual and facial (5th and 7th cranial) nerves from the anterior two-thirds of the tongue and via the glossopharyngeal (9th cranial) nerve from the posterior one-third

of the tongue The arrangement is obviously a convenient one from the functional standpoint, since the 9th nerve, carrying afferent fibers from the posterior part of the tongue, also carries the afferent secretory fibers for the more posterior salivary glands (parotid); the lingual and facial nerves which contain the taste fibers from the anterior portion of the tongue also carry the secretory fibers (chorda tympani) to the more anterior salivary glands (submaxillary and sublingual)

The sight, smell or thought of food causes secretion of saliva, impulses passing down from the respective cerebral areas to the salivary centers in the medulla These stimuli are much less effective than the actual tasting of food Mechanical stimulation (irritation) of the mouth, pharynx or esophagus induces salivation, the afferent pathways being the trigeminal (5th cranial), glosso-pharyngeal (9th cranial) and vagus (10th cranial) nerves respectively Tumors of the esophagus often cause profuse salivation by this reflex mechanism. Tonsillectomy under local anesthesia and irritation of the mucous membrane of the mouth by ether vapor likewise induce salivation reflexly

RELATION OF SALIVARY FLOW TO THIRST

When 300 cubic centimeters of 5 per cent sodium chloride is injected intravenously in man, thirst results which is associated with a reduction in salivary flow Following this injection there are changes in serum concentration of sodium chloride and protein indicating an increase of 5 to 10 per cent in plasma and extra cellular volumes When 400 to 600 cubic centimeters of water is taken by mouth prior to the salt injection the severe thirst is alleviated and reduction in salivary flow prevented Nevertheless, rise in serum chloride concentration and fall in serum protein are of the same degree as in the other experiments, suggesting that thirst and salivary flow are sensitive to fluid changes which are not measured by such indices as changes in serum concentration of protein chloride and sodium (Holmes and Gregersen, 1947)

FUNCTIONS OF SALIVA

The chief functions of saliva are to dissolve or lubricate the food, and to initiate the digestion of certain carbohydrates The former action seems to be the more important The saliva is apparently not absolutely essential for good health, for dogs from which all the salivary glands have been excised have remained healthy over long periods of time Such dogs do not drink any larger quantities of water than normal dogs, hence the sensation of thirst is not as largely dependent upon a deficiency of saliva as was formerly believed In man the saliva may be

of considerably more importance, for Jackson observed that children with esophageal obstruction being fed by a gastrostomy tube failed to gain in weight until dilatation of the esophagus had been sufficient to permit saliva to pass into the stomach or until the lost saliva was returned by tube Saliva has apparently no important antiseptic action, though it destroys tetanus toxin and snake venom Mouth wounds heal just as well in dogs in which the salivary glands have been extirpated as in normal dogs The average daily secretion of saliva in man is about 1,500 cubic centimeters

SWALLOWING

The voluntary act which initiates swallowing consists of elevation of the floor of the mouth, mainly by contraction of the mylohyoid muscles, and retraction of the tongue As a result of these voluntary movements, a series of coordinated movements of the muscles of the pharynx and esophagus occur by a reflex mechanism, independently of the will The adequate stimulus for the completion of the act is the initial voluntary movements The presence of an object to be swallowed in the pharynx or esophagus does not dispense with the necessity for these movements, the action of the mylohyoid muscles and tongue occurs first, and then, by reason of afferent impulses from these voluntary muscles, the pharynx and esophagus complete the remainder of the swallowing act reflexly and carry the object to the stomach

The act of swallowing involves elevation of the whole larynx and can not be carried out if the larynx is not free to move, as for instance in some cases of carcinoma of the larynx. The epiglottis can be partly or completely absent without impairment of the act of swallowing There seems to be a "swallowing pattern" in the medullary centers of the motor nerves concerned (9th, 10th and 12th cranial), as the result of appropriate excitation an impulse is generated in this "swallowing center," the impulse spreads throughout the pattern and causes the complex group of coordinated muscular movements which constitute the act of swallowing Mechanical stimulation of the esophagus by an object within its lumen does not give rise to peristalsis of the esophagus The object reflexly excites the secretion of saliva as described above and peristalsis of the esophagus is only instituted in consequence of the swallowing of the saliva

There are several different sensory areas and corresponding afferent pathways for the instigation of swallowing Mechanical stimulation of portions of the soft palate (5th and 9th cranial nerves), the posterior pharynx (9th nerve) and the epiglottis (10th nerve) excites the de

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under conditions which excite nausea or vomiting, it is mediated through the medullary center which controls esophageal movements

After vagotomy in dogs, regurgitation and emesis is a common consequence, due apparently to paralysis of the esophagus with retention of food The vomiting apparently results from irritation of the pharynx by the large amount of retained material This response to irritation is more sensitive in many dogs after than before vagotomy

In complete obstruction of the esophagus a marked fall in blood chloride occurs The blood changes are more marked and the course is more rapidly fatal than in pyloric or high intestinal obstruction (Haden and Orr, October, 1923)

THE STOMACH

The stomach is divided into two functionally different parts The cardiac part to the left of the incisura angularis, consisting of the fundus and body, produces the hydrochloric acid but has relatively less motility than the pyloric part The latter, consisting of the pyloric antrum and canal, is much more motile but secretes only mucus The first portion of the duodenum ("the cap") is functionally integrated with the pyloric part of the stomach

GASTRIC MOTILITY

Nervous Control of Gastric Motility The stomach as a whole possesses tone, that is, its wall is constantly in a state of partial contraction, apart from peristaltic activity This tonus is controlled by the intrinsic nerve plexus in the wall of the viscus and is independent of the extrinsic nerve supply By changes in the degree of tonus, effected by means of the intrinsic nerve plexus, the stomach adapts its capacity to the volume of its contents so as to offset changes in intragastric pressure which would otherwise occur according to the degree of filling or emptiness of the organ

The vagus is the motor nerve to the stomach Experimental stimulation of the vagus yields variable results depending mainly upon the state of contraction of the stomach at the time the stimulus is applied If the stomach is relaxed, vagus stimulation causes it to contract and vice versa or one part may be caused to contract and another part to relax Bilateral vagotomy in the monkey was found by Ferguson to result in persistent cardiospasm and gastric hypotonia with delay in the onward movement of solid foodstuffs

In dogs the vagus contains both inhibitory and motor fibers to the cardiac end of the stomach The inhibitory fibers apparently branch

glutition reflex Deglutition will therefore be deranged by any lesion of these areas or nerves, or of the corresponding medullary nerve centers

THE ESOPHAGUS

Peristalsis of the esophagus is dependent upon the nerve plexus on the surface of the organ and does not occur when the nerve supply is removed With each downward wave the cardia opens, the relaxation of the so-called cardiac sphincter being coordinated with the esophageal movements through the esophageal nerve plexus After a series of swallows in quick succession the cardia remains relaxed and patent for some time Stimulation of the vagus causes at first relaxation of the cardia, followed by strong contraction X-ray shows that a well lubricated bolus of food normally passes through the cardia from 8 to 18 seconds after it is swallowed When the coordinating mechanism fails to function cardiospasm results Stimulation of the normal pharynx induces relaxation of the cardia Correspondingly, spasm of the cardia seems to be related to anaesthesia of the pharynx with absence of the gag reflex, both are perhaps dependent upon a functional derangement of the medullary centers of the 9th and 10th cranial nerves Some cases of cardiospasm may perhaps be due to a true paralytic condition of the vagus supply to the esophagus, for dividing the vagus causes increased tone of the cardiac sphincter and dilatation of the esophagus Both epinephrine and acetyl choline cause contraction of the cardia Cardiospasm following division of the vagus nerves in the neck is probably due to interference of the inhibitory mechanism and preponderance of the sympathetic innervation which is motor in its effect on the cardia (Lehmann, 1945)

The Cardiac Sphincter · The cardiac sphincter is an indefinite muscle anatomically A pressure from above of only 5 to 7 millimeters of water is sufficient to cause it to open, whereas pressure from the gastric side induces spasm, and must rise to 50 millimeters of water in order to cause the sphincter to open

The mechanism of closure of the sphincter is unknown One theory ascribes the closure to increase in gastric acidity while another theory is that a rise in intragastric pressure is responsible for closure of the sphincter In any case it is known that strong stimulation of sensory nerves of the abdominal viscera experimentally induces cardiospasm reflexly via sympathectic afferent pathways When a caustic substance is swallowed the irritation it produces causes spasm of the cardia so that the substance is held in the lower end of the esophagus for a while, predisposing to stricture formation at that level Reverse peristalsis occurs

duodenum At a later stage in digestion, the pylorus may open also between waves and regurgitation of alkaline duodenal contents into the stomach may occur The pylorospasm associated with ulcer must prevent this normal regurgitation (and neutralization) to some extent The exact mechanism of opening and closure of the pyloric sphincter is unknown

The pylorus obeys the law of the intestine in general, but it seems that stimuli resulting from the presence of material or from increased tension on its duodenal side are prepotent over stimulation on the gastric side, that is, the valve does not open readily as long as the duodenal bulb contains material Moreover the duodenal bulb undergoes rhythmic contractions independent of stomach contractions It appears also that some factor related to the consistency of the food material influences the action of the valve, although it has no effect upon gastric motility itself

Gravity is not a factor in the emptying of the stomach and should not be given any consideration in selecting the site of the stroma in performing gastroenterostomy Acidity is no longer thought to play an important role in the normal regulation of the pyloric valve No other liquid leaves the stomach as rapidly as water Temperatures of the ingested material from 2 to 50° C have little effect on the emptying time of the stomach

It is known that stimulation (irritation) of the afferent nerves from any abdominal viscus (gallbladder, appendix) may cause reflex contraction of the pylorus and also widespread disturbances in the tone and motility of the stomach For example, belching of swallowed air, frequently the only symptom of gallstones, is probably due to disquietude of the gastric musculature reflexly induced Maddock has demonstrated that in certain individuals of nervous temperament due to relaxation of the constrictor muscles of the pharynx, air passes freely into the stomach in large amounts During anesthesia with the aid of respiratory movements the amount of air entering the stomach may reach enormous proportions to such an extent that perforation of the stomach has been known to occur Gas passes through the stomach and through the entire intestinal tract very rapidly, frequently traversing the entire alimentary canal in 24 to 30 minutes

A localized spasm of the stomach does not necessarily indicate that there is an organic lesion opposite the point of spasm The lesion may be elsewhere in the abdomen, or the spasm may be purely "functional" and disappear under massage and belladonna Prolonged spasm, as in hypertrophic pyloric stenosis in male infants, leads to work hypertrophy

off from the main vagus trunk above the level of the arch of the aorta and take an intrinsic course in the wall of the esophagus to the cardia (Hwang, Essex and Mann, 1947) Vagotomy also abolishes the gastric motor response to insulin Insulin increases the food intake in both normal animals and animals with extrinsically denervated stomachs If the increased food intake were due to the stimulation of gastric motility by insulin, then it would not be expected to occur after vagotomy It therefore seems probable that insulin hypoglycemia acts directly on the brain to excite food taking activity (Grossman and Ivy, 1947)

Resection of the vagus nerves in man results not only in a reduction in gastric acidity but also in gastric hypotonia. The relief of pain in peptic ulcer is presumably brought about by release of gastrospasm as well as a decrease in gastric secretion

The sympathetic innervation of the stomach is presumably inhibitory, but marked inhibitory effects have not been demonstrated clearly, the response varies according to the state of the organ at the time, just as in the case of the vagus It is believed that the chief function of the sympathetic fibers to the stomach is to control the blood vessels of the viscus Special hormonic control of gastric motility has not been demonstrated

When the composition of a basic oatmeal test meal is changed isocalorically by replacing parts by fat, protein or carbohydrate, there is no significant alteration in gastric motility (Henschd, *et al*, 1947) D-amphetamine sulfate produces a transient depression or abolition of gastric hunger contractions when administered parenterally to intact dogs, but has no effect on the gastric motility of vagotomized dogs (Sangster, Grossman and Ivy, 1948)

Normal Gastric and Pyloric Motility · In the fasting stomach there are brief rhythmic increases of tone about every twenty seconds, and at longer intervals there occur more powerful so-called hunger contractions, each of which may last 30 seconds The hunger contractions are confined to the fundus While the stomach is empty, the pylorus may be closed or open, sometimes remaining open for many minutes at a time After the taking of food, peristaltic waves occur, a wave starting high on the body of the stomach about every 20 seconds and moving toward the duodenum The fundus and uppermost portion of the body do not take part in these peristaltic movements At first the waves do not proceed as far as the pylorus, which remains closed After about 5 to 10 minutes some of the waves proceed farther along the pyloric antrum and canal and each time this occurs the pylorus opens for a moment, permitting a small amount of gastric contents to pass into the

duodenum At a later stage in digestion, the pylorus may open also between waves and regurgitation of alkaline duodenal contents into the stomach may occur The pylorospasm associated with ulcer must prevent this normal regurgitation (and neutralization) to some extent The exact mechanism of opening and closure of the pyloric sphincter is unknown

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of the muscle above the stenosis The three motor factors which determine the speed of emptying of the stomach are the tone of the stomach wall, peristaltic movements and the activity of the pylorus Morphine may cause pylorospasm.

Gastric and intestinal peristalsis immediately after operation was studied by Matyas by means of x-ray examinations following barium sulphate administration by mouth Emptying of the stomach was found to be delayed for at least ten hours, and after operations on the stomach, for fifty-two hours

Gastric emptying time in dogs was shown by Mecray, *et al*, to increase as the serum protein content decreased, whether the stomach was intact or operated upon This result was attributed to nutritional edema, for all the dogs having plasma protein of 4 per cent or lower showed gross edema of the stomach at postmortem or operation The normal plasma protein content is 7 per cent, the critical level for manifest edema is 5 2 grams per 100 cubic centimeters blood, although this is a variable figure in different individuals If the sodium ion is restricted it is hard to cause edema in either dogs or man, regardless of the plasma protein level

The sensations of hunger, appetite and repletion are controlled fundamentally by the state of nutrition, though hunger seems to be related especially to contractions of the empty stomach The sense of repletion is perhaps partly dependent on increase of intra-gastric or intra-abdominal tension as reported to the brain by afferent visceral nerves from the splanchnic region and somatic nerves from the parietes When varying amounts of water were included in the diet of dogs, it was found by Archdeacon and Allen that increasing the water content facilitated ingestion yet ingestion of food without addition of water did not affect appreciably the urge to drink Similarly, albino rats when furnished with food mixed with varying amounts of cellulose, kaolin and water could be induced to eat roughage up to 8 per cent of their body weight per day and water up to 125 per cent per day Compromise was effected by the rats between an excessive amount of alimentary filling and diminished amount of nutrients After complete deprivation of food or water or both for one to six days body weight was later slowly restored by the consumption of very small excesses of food (Adolph, 1947)

Vomiting *Mechanics of Vomiting* Retching and vomiting consist essentially of contractions of certain respiratory muscles in abnormal sequence, rather than of reversed peristalsis in the stomach or esophagus It is true that antiperistalsis may occur as part of the mechanism of

vomiting but during the actual expulsion, the stomach is flaccid and the cardiac sphincter is relaxed The expelling force is supplied by a simultaneous contraction of the muscles of the diaphragm and abdominal wall Material remaining in the esophagus is then ejected by contraction of the thoracic cage, aided perhaps by an antiperistaltic wave in the esophagus itself

Vomiting Center Since the motor nerves involved in the act of vomiting are those of the stomach and esophagus (vagus chiefly) and of the respiratory muscles, it is not surprising that a so-called vomiting center in the medulla has been located near the vagus and respiratory centers, though its exact limits have not been determined It seems reasonable to suppose that a "vomiting center" does not exist as such but is identical with the vagus and respiratory centers, vomiting resulting from disturbed functioning of these normal centers Dogs frequently develop regurgitation and vomiting after vagotomy at and especially higher than the hilus of the lung This is apparently due to paralysis of the lower two-thirds of the esophagus, increased irritability of the pharynx and irritation impulses from the pharynx due to accumulated food in the esophagus.

Nystagmus is referable to disturbed functioning of the oculo motor centers, not to a "nystagmus center," sneezing to disturbed functioning of the respiratory center, not to a "sneezing center," etc If every functional motor and secretory disturbance required the existence of a separate center in the brain, we would have to postulate a "constipation center," "hypochlorhydria center" and a host of others, whereas it is simpler and more logical to refer these conditions to the same centers which control the involved organs under normal conditions

Nervous Factors in Vomiting Innumerable types of stimuli in various parts of the body can give rise to afferent impulses capable of exciting vomiting by their action on the medullary centers It has been mentioned that the functioning of the circulatory and respiratory organs is regulated continuously and predominantly by afferent impulses arising in certain portions of the circulatory and respiratory systems themselves, respectively, afferents from other regions exerting a controlling influence only occasionally or under exceptional circumstances In a similar manner, afferent pathways from the stomach itself and from other portions of the alimentary system predominate somewhat over those from the rest of the body in the regulation of the motor activity of the stomach

Though stimuli initiated by lesions anywhere in the abdominal cavity

very readily cause vomiting, lesions of the gastro-intestinal tract and its associated digestive organs seem to induce vomiting more readily than those of the other abdominal viscera

Chemical Factors in Vomiting The medullary centers which mediate the vomiting movements can be stimulated directly by chemical abnormalities of the blood bathing it, such as asphyxial changes and circulating drugs or poisons, either endogenous or exogenous Even mechanical pressure upon the center in cases of increased intracranial pressure can provoke vomiting, though it is likely that the pressure induces asphyxia of the center by interfering with its blood supply, the asphyxia being the immediate stimulus for vomiting

GASTRIC SECRETION

Chemical Composition of Gastric Secretion· Hydrochloric acid, the chief constituent of gastric secretion, is produced mainly in the fundus and body of the stomach, but also in the pyloric region The exact chemical mechanism of its manufacture is unknown Its chief function is to promote the action of pepsin The existence of rennin as a separate ferment is disputed By using the phenomenon of the digestibility of rennin by pepsin as a basis for the detection of rennin, it was found by Dotti and Kleiner that no rennin was present in the gastric juice of human adults The other functions of gastric HCl are to hydrolyze disaccharides, to destroy bacteria and to aid in stimulating the secretion of bile and pancreatic juice The total chloride content of gastric juice is made up of three fractions, free HCl, combined HCl and inorganic chloride The last is either secreted as such by the stomach mucosa or is formed from gastric free HCl by combination with alkali regurgitated from the duodenum The distribution of chloride among the three forms will vary according to the amount of protein present, the amount of regurgitation through the pylorus and other factors, hence at any given time the total chloride is the truest guide to the total HCl secreted. Citing the previous contradictory results as to the relative roles of bile, pancreatic juice and intestinal juice in the neutralization of gastric acidity, De Bakey from experiments on dogs concluded that bile is the most effective factor in preventing jejunal ulcer, and intestinal juice the least effective

Gastric Contents Gastric "contents" consist of gastric secretion plus variable amounts of saliva and regurgitated duodenal and pancreatic secretions and bile The fasting total acidity normally is 0 43 to 0 6 per cent and free HCl 0 4 to 0 5 per cent One and one-half hours after a test meal there is normally only about 0 1 per cent free HCl, which

is equivalent to 30 cubic centimeters of N/10 NaOH per 100 cubic centimeters of gastric contents This decrease in the percentage of free HCl is associated with a corresponding rise in the inorganic chloride content of the stomach, this indicates that reflux of alkali through the pylorus occurs in the latter stages of gastric digestion, the pylorus remaining open between the peristaltic waves of the stomach If the opening of the pylorus between the gastric waves fails to occur, a "climbing type" of acidity curve is produced If the opening occurs too early, free hydrochloric acid becomes low or absent, but the inorganic chloride correspondingly increases In such cases the stomach is usually atonic.

It is apparent, then, that the acidity of the gastric contents depends upon (1) the amount of acid secreted, and (2) the behavior of the pyloric sphincter The terms hyper and hypochlorhydria refer to gastric "contents" and do not convey accurate information as to the amount of HCl in the gastric juice as secreted.

Constancy of Chloride Concentration Gamble and McIver (1928) studied the composition of gastric secretions from different parts of the stomach by means of isolated pouches of the fundus and pylorus of the stomach of the cat They found that in the fundus chloride is secreted at a quite stationary concentration of about 165 cubic centimeters 0 1 N HCl per 100 cubic centimeters of secretion, whereas the concentration of basic ions varies widely, probably because of the admixture at different times of different amounts of mucus secretion from the fundic glands The variation in acidity, as measured in terms of hydrogen ion concentration, in the secretion of the fundus of the stomach is therefore referable to changes in fixed base and not to changes in HCl secretion From the pyloric part of the stomach an alkaline secretion containing more fixed base than chloride was obtained In the presence of irritation more mucus is secreted, therefore more fixed base is lost together with the loss of chloride In the blood plasma conditions are just the reverse of those in the fundus of the stomach, for in the blood the concentration of fixed base remains stationary, the acid factor being adjustable because of the ability of HCO_3 to substitute for chloride

Hyperacidity In clinical hyperacidity the concentration of HCl in the gastric contents seldom approaches and never exceeds the normal acidity of pure gastric juice Hyperacidity is probably never due to the production of actually hyperacid juice It results from either the secretion of an excessive amount of normal juice or a lessening of the normal diluting and neutralizing factors Hyperacidity is often associated with some delay in emptying of the stomach Gastric symptoms do not

parallel the degree of hyperacidity Achlorhydria, that is, absence of HCl, when once developed, is permanent It is often associated with rapid emptying of the stomach In about 5 per cent of normal individuals, no HCl whatever is secreted by the stomach, this achlorhydria being probably congenital In carcinoma of the stomach there may be some production of HCl, but often the acid can be detected only after the increased amount of mucus has been washed away The production of hydrochloric acid is directly proportional to the number of normal appearing parietal cells present in the fundus mucosa. The number of such cells is directly dependent upon the degree of chronic atrophic gastritis present (Stewart and Guiss, 1948) It, therefore, appears that the degenerative changes of chronic atrophic gastritis may be the basic cause of hypo-acidity and anacidity in gastric disease Achylia gastrica is absence of both HCl and enzymes, in this condition liquid and mucus may still be secreted

Rehm and Hokin have demonstrated that the electrical potential difference across the stomach wall is related to the secretion of hydrochloric acid Pilocarpine or mecholyl administration in dogs produces a decrease in the gastric potential associated with the onset of secretion of hydrochloric acid After the initial potential decrease there is little change although the secretory rate may increase considerably After secretion is initiated by pilocarpine, atropine will decrease it again and raise the gastric potential Ethyl alcohol applied to the mucosa of the stomach for certain periods did not in their experiments result in secretion of hydrochloric acid The potential, however, was lowered In histamine stimulated stomachs marked lowering of the gastric potential was always associated with marked lowering of the secretory rate

There is no definite relation between the secretion of acid, ferments and mucus The factors which control secretion of mucus by the stomach are unknown Mucus cannot be the chief factor which protects the gastric mucosa from HCl Antipeptic and antitryptic ferments have been isolated from the stomach and intestinal mucosae and from their mucus

Histamine and Gastric Secretion In a study of a large series of normal persons subjected to histamine test meals, Polland found that the maximum 10 minute volume of gastric secretion in men ranges from about 40 cubic centimeters at 25 years of age down to about 25 cubic centimeters at 65 years of age It is about 15 per cent lower in women The total gastric secretion declines with age at about the same rate as the maximum 10 minute volume The total acidity ranges from 100 units for men and 80 for women at 25 years of age down to about 65

units in both sexes at the age of 65 years The incidence of anacidity for normal men is about 10 per cent and for normal women 14 per cent. There is a steady increase in the incidence of anacidity from youth to old age This fact should be borne in mind in interpreting the finding of anacidity in cases of suspected gastric carcinoma In approximately 90 per cent of cases of duodenal ulcer and gastric ulcer the total acidity is higher and in about 80 per cent the volume of secretion is greater than the normal mean values for the age and sex of the individual In cases of carcinoma of the stomach approximately 70 per cent have anacidity and very few indeed have volumes or acidity above the mean normal value for the age and sex of the individual No evidence has been found that any particular disease, except pernicious anemia, is associated with a characteristic type of gastric secretion

Trach, Code and Wangensteen, in studies upon the histamine activity extractable from human gastric mucosa, found that the fundic mucosa extracts contained 3 5 to 24 1 milligrams of histamine per kilogram of fundic mucosa or an average of 10 2 Antral mucosa contained an average of 5 8 milligrams of histamine per kilogram of mucosa On subsequent injection of these extracts into dogs with Heidenhain pouches all of the extracts produced a prompt secretion of acid gastric juice The crystalline form of histamine has never as yet been isolated from gastric extracts

When four or five histamine injections are given at intervals of 45 minutes to individuals with gastric hypersecretion, as much as 4 grams of chloride can be secreted by the stomach in 3¾ hours In patients with achylia, up to 2 5 grams of chloride, mostly in the form of neutral chlorides, is eliminated under the same conditions Secretion of neutral chlorides, therefore, can be promoted by histamine stimulation even in cases in which free HCl is absent.

The parietal cell of the stomach appears to be the most sensitive to histamine of any cell in the body though this is sometimes equalled by that of cerebral vessels The parietal cell alters the plasma passing through it to produce hydrochloric acid and thus acid flow is partly dependent upon an adequate blood supply Histamine, however, seems to have a specific effect on the cell as well as a vasodilating effect (Hanson, Grossman and Ivy, 1948)

In some persons particularly those with achylia, increased elimination of urine following histamine injection is so noticeable that it seems as if the kidneys are stimulated instead, when the response of the gastric glands is insufficient Chloride secretion by the kidneys in response to histamine is especially marked in persons in whom chloride

secretion by the stomach is high, the urine becomes more alkaline in these cases

Neutral Red Test of Gastric Secretion Held has shown that when neutral red is injected intramuscularly, the normal gastric mucosa eliminates the dye in from 12 to 24 minutes after injection In hyperchlorhydria it is retarded (26 to 40 minutes) If elimination of the dye by the kidney is impeded owing to renal disease, there is a compensatory acceleration of the excretion by the gastric mucosa, independent of the gastric acidity The elimination is increased in gastric and duodenal ulcer In gastric cancer it is diminished but it may be unchanged when the cancer is localized in the pyloric region Held believes that the test is superior to the histamine test for determining the secretory function of the gastric mucosa in achlorhydria

Abnormalities Related to Gastric Secretion *Chloride Loss and Alkalosis in Obstructions* MacCallum, *et al* (1920), found that the decrease in blood chlorides which occurs following loss of gastric juice by vomiting in pyloric obstruction can be prevented readily by the early administration of a large amount of chlorides but cannot be corrected easily once it has developed Even when the plasma chloride concentration has diminished considerably the gastric mucosa still is able to secrete hydrochloric acid

Duodenal obstruction produces the same chemical changes in the blood as duodenal fistula, namely alkalosis, decreased concentration of chlorides and increased concentration of urea That sodium chloride is a valuable therapeutic aid in pyloric and high intestinal obstruction was shown experimentally by Haden and Orr (July, 1923) In duodenal obstruction, the administration of salts other than NaCl is of no benefit for the correction of the chemical changes in the blood Various salts which have been tried experimentally by Haden and Orr (1924) are KCl, $CaCl_2$, $MgCl_2$, $NaSO_4$, sodium citrate and sodium phosphate In duodenal fistula Walters, *et al* (1926), found that restoring the normal blood chloride concentration by the intravenous injection of strong NaCl solution did not prolong life, benefit was obtained only if, in addition, an adequate amount of water was given

Sodium Loss and Total Electrolyte Concentration Loss of chloride alone causes alkalosis but it does not necessarily diminish the total ionic concentration of the body fluids because the chloride is easily replaced by the ever-available HCO radical Loss of sodium, on the contrary, does deplete the total ionic content of the body for it is not replaceable by any other base, its effect is in fact doubly harmful because for a given amount of sodium lost, an equivalent amount of some acid radical,

chiefly HCO_3, must be lost with it, for base is an indispensable anchor for chloride and bicarbonate Since, for maintenance of the normal osmotic pressure of the body fluids, the volume of water which the body can hold depends on the total quantity of dissolved electrolytes, regardless of their nature, loss of sodium is the most important factor in causing dehydration in pyloric obstruction The dehydration cannot be relieved by water or chloride ions alone, sodium chloride is efficacious not because of its chloride but because of its replacing lost sodium Dehydration connotes the loss of the particular electrolyte, sodium, and this ionic loss is of graver import than the loss of water itself In the treatment of dehydration, the replacement of the lost electrolytes is essential.

In pyloric obstruction the loss of chloride is conspicuous and well known, but it is a fact of importance that vomiting causes the loss of a considerable amount of sodium as well as loss of chloride Analyses of 24-hour collections of vomitus in experimental pyloric obstruction in the dog showed that sodium is lost in amounts equal to more than half the chloride loss (Gamble and Ross, June, 1925)

Reduction of Blood Volume in Obstruction In pyloric obstruction in the rabbit, Gamble and McIver (August, 1925) found that though the maximal reduction of blood volume was only 30 to 40 per cent, this loss represented only a small fraction of the total amount of fluid actually withdrawn from the body More than twice the initial plasma content of water was found to enter the stomach from the blood before death occurred The amount of fixed base entering the stomach was equivalent to more than three fourths the quantity of chloride lost There was no appreciable loss of K, Ca or Mg into the stomach in pyloric obstruction After duodenal obstruction however, considerable amounts of K were lost into the stomach and duodenum The ultimate decline of the vital function and death in gastrointestinal obstructions are probably dependent partly on lack of plasma repair

Digestive Alkalinuria Bence-Jones, who was the first to observe that in the post-digestive period the reaction of the urine becomes alkaline, assumed that the acid withdrawn from the blood by the stomach for digestion left an excess of alkali which had to be removed through the kidneys If this is true, then when acid secretion is absent, as may be the case after gastrectomy, the post-digestive alkalinity of the urine must likewise remain absent The urines of 30 patients who had undergone gastric resection were examined by Lion He found that digestive alkalinuria was absent in all cases

Gastrectomy Anemia Instances of severe anemia following extensive

gastrectomy in man have been reported but they are uncommon There appears to be a marked species difference in this regard, for total gastrectomy is regularly followed by anemia in the hog, but not in the dog The concentration of the substance effective against pernicious anemia in dog's liver is only about one-fifth that in the livers of the hog, horse and cattle It appears that gastric function in man and in the dog does not play the same part in hematopoiesis that it does in certain other species

Meyer, *et al*, pointed out that pernicious anemia has followed not only extensive gastric resections but also partial resections, gastroduodenostomies and gastrojejunostomies They reported a case following total gastrectomy

After stomach resection slight to moderately severe anemia of the secondary type occurs in about 20 to 35 per cent of cases The tendency to anemia is much greater in women than in men and is especially marked in younger women Dedichen advises that this fact be taken into account in selecting the type of operation for a peptic ulcer in a young woman In the majority of the cases the anemia does not give rise to severe symptoms There is no evidence in the available data that one method of partial gastrectomy is more likely to be followed by anemia than another A definite relation of the anemia to the gastric operation is indicated by the fact that a certain number of cases of hypochromic anemia occurs postoperatively in men, whereas idiopathic anemia of this type in men is so rare as to be considered a curiosity However, the occurrence of anemia is independent of the amount of stomach removed The nature of the disturbance of the gastro-intestinal function responsible for the anemia is not known, but rapid gastric and small-intestine evacuation is common Achlorhydria is not necessarily a factor, for normal acidity or hyperacidity has been found in a certain proportion of cases following resection even when severe anemia was present Increased amounts of fat in the feces are common, but it is not possible to correlate the occurrence of anemia with any specific changes in the feces

The importance of the diet has been pointed out by Hartfall, who surveyed the diet in severe cases and found it inadequate for maintenance of normal blood regeneration Extreme modifications of the diet, usually adopted to offset gastrointestinal symptoms, were encountered, and in most cases the diet was grossly deficient in both mineral and vitamin content The results of treatment with liver and iron, according to the type of anemia present, are satisfactory The addition of vitamins may sometimes cause further improvement Gastric resection alone is not believed to lead to pernicious anemia

Gastric Lavage There is no absorption of water or saline solution in the stomach There is definite evidence of absorption of ethyl alcohol from the stomach of rats, the amount of alcohol absorbed being related to hypostatic or filtration pressure Under experimental conditions, about 14 4 milligrams of ethyl alcohol per hundred grams of body weight may be metabolized by a rat in 20 minutes (Karel and Fleisher, 1948) Since there is no absorption of water or saline solution in pyloric stenosis, dehydration cannot be prevented or to any degree alleviated by gastric lavage In pyloric stenosis, therefore, dehydration cannot be prevented or to any extent alleviated by gastric lavage, except insofar as lavage tends to check secretion of gastric juice, which it appears to do Following operative pyloric obstruction in cats, Freeman and Brown found that the animals which were subjected to repeated emptying of the stomach survived considerably longer than untreated controls When a mixed diet of meat and milk was given, emptying and washing out the stomach allowed the animals to live almost twice as long as those which accumulated secretions in the stomach and then vomited spontaneously

Factors which normally hasten secretion of water and electrolytes by the stomach are distention, salts and nitrogenous substances, water itself does not stimulate gastric secretion Repeated gastric lavage, by removing any excitants of secretion and preventing distention, caused a decrease in the average daily loss of water and chloride per unit of body weight, and a higher level of chloride in the blood The improvement in general condition after gastric lavage seems to be due at least in part to this reduction in the rate of loss of water and electrolytes from the body into the lumen of the stomach

Carlson and Orr, similarly, found that dogs with experimental obstruction of the jejunum, if given water freely, lost less weight and lived twice as long as dogs given no food or water, even though the blood chemical changes (Cl, CO_2, sugar) were greater in the dogs given water They concluded that continuous gastric lavage is beneficial in acute intestinal obstruction

Paine *et al*, on the contrary found in postoperative distention that large oral intake of fluid during duodenal suction enhanced the chloride loss When 2,000 cubic centimeters of fluid was given to the patient by mouth, approximately 1 5 grams of sodium chloride was removed by aspiration through the duodenal tube when 4,000 cubic centimeters of oral fluid was given, the loss of chloride was approximately 3 5 grams

Constant Gastric Suction From a study of constant gastric suction with the Wangensteen apparatus in clinical cases, Sullivan concluded that it would be almost impossible to produce alkalosis and death unless

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secretion, probably reflexly Mechanical stimulation of the gastric mucosa, however, e g, by a rubber tube, does not induce gastric secretion of any kind In acute dilatation of the stomach, the large amount of fluid present in the stomach is usually alkaline, being derived from the duodenum (Dragstedt) With increase in size of the stomach, pressure upon the celiac ganglion causes increased hypertonia of the stomach wall as well as generalized sweating and a shock like state

Gastric Centers Cushing points out that those favorably disposed toward the neurogenic conception of peptic ulcer have gradually shifted the burden of responsibility from the peripheral vagus to its center in the medulla, then to the midbrain, and then to the interbrain (diencephalon), which has become recognized as an important station for vegetative (parasympathetic) impulses easily affected by psychic influences Gastric erosions, perforations or ulcers may be produced by experimental lesions of this region or of the fiber tracts extending from it

Chemical Control of Gastric Secretion The chemical control of gastric secretion is not completely understood The presence of acids of various kinds in the stomach leads to secretion of gastric juice Foods, particularly proteins, stimulate secretion, not by direct mechanical stimulation of the stomach mucosa, nor by reflex action, but by forming digestion products which stimulate the mucosa directly or possibly act upon the local intrinsic nerves or their endings That a humoral mechanism may take part in the control of gastric secretion is proved by the fact that in a gastric pouch transplanted to some other part of the animal's body secretion takes place following ingestion of a meal This effect still occurs when all nervous connections between the stimulated portion of the stomach into which food enters and the portion responding with secretion have been interrupted (Grossman *et al*, 1948) Anti-pernicious anemia liver extract is rich in material having gastric secretogogic potency This substance stimulates gastric secretion on local application to the gastric and intestinal mucosa, although this stimulation is not as great as that produced by pilocarpine Grossman Wolley and Ivy believe that histamine could be the hormonal agent responsible for the substantial increase in pepsin noted after a meal

Gastrin Gastrin is the name given to a hypothetical secretogogue supposed to be formed in the mucosa of the pyloric portion of the stomach as the result of the action of hydrochloric acid on this mucosa It is supposedly absorbed into the blood stream and carried through the systemic circulation to the fundus and body of the stomach where

there were complete obstruction at the pylorus or gastric stoma With such obstruction he found that alkalosis resulted after five to eight days of suction unless sufficient parenteral saline was administered Northrup found that continuous drainage of the stomach and duodenum by suction produced marked changes in the composition of the blood (decrease in chlorides, increase in CO_2 combining power and elevation of the hemoglobin content and red cell count), but few if any untoward symptoms Continuous venoclysis was effective in controlling these blood changes Administration of the aspirated intestinal contents as retention enemas did not cause irritation, but its therapeutic value was not determined Roberts has recommended this replacement treatment in cases of acute mechanical ileus

Nervous Control of Gastric Secretion The stomach mucosa secretes gastric juice continuously during fasting, even after division of both vagus nerves The rate of fasting secretion is not constant, varying between 10 and 60 cubic centimeters per hour The mechanism by which this spontaneous secretion is effected is unknown, the fact that it occurs suggests that the chief function of the extrinsic nerves which normally regulate gastric secretion (the vagi) is merely to correlate the secretory activity of the stomach with events occurring in the rest of the body

Various influences affect the vagus center so as to cause increased or decreased gastric secretion Certain psychical influences from the higher centers of the brain by their action upon the vagus center markedly inhibit secretion Appetite, which is accentuated by the thought, sight, smell or taste of food, induces (via the vagi) increased gastric secretion, the socalled appetite juice Taste is the most effective of these stimuli That pathological elevation or depression of the threshold for the taste of salt can exert an influence on the sodium chloride and therefore on the water exchange of the body is suggested by Hansen and Langer on the basis of their study of changes in the sense of taste during pregnancy Appetite juice secretion continues for only about 15 minutes It is not essential to health and is apparently of minor importance in man

An average meal normally causes the secretion of about 700 cubic centimeters of gastric juice, which is produced over a period of about five hours Various lesions in the alimentary tract, such as cholecystitis and appendicitis, reflexly induce increased or decreased gastric secretion, but this effect is not constant or predictable and is therefore not of diagnostic value

Distention of the stomach, as in pyloric obstruction, induces copious

acidity depends on the amount of fundus removed For permanent benefit in the treatment of duodenal ulcer he stresses the importance of a reduction in the volume of gastric secretion, rather than a reduction in the degree of acidity

Somervell and Ore in 1936 reported beneficial results following the ligation of a large part of the blood supply of the stomach These beneficial results were apparently due to a marked fall in acidity which these authors reported lasted for five or six years Wood, on repeating this work reported a decrease in acidity, but the amount of acid secreted returned to normal within six to 15 months He reported stoma ulceration in three of the 47 cases

Complete pancreatectomy in dogs is followed by the secretion of an excessive amount of gastric juice of normal acidity

Ferguson summarizes briefly the data regarding regulation of gastric acidity which indicate that the acid bearing ("oxyntic") cells secrete in an "all-or nothing" manner, depending on the concentration of electrolytes in the circulating blood, so as to maintain ion equilibrium between the gastric contents and the blood supply The chief regulating factor then is the need for maintaining an osmotic balance Superimposed on this basic condition, however, are other mechanisms which permit altered rates of activity, namely (a) local stimulation of the stomach wall itself by food or by its products, (b) hormonal influences (e g, "gastrin") acting by way of the blood stream and (c) secretory nerve impulses, psychic or reflex

The predominance of the osmotic mechanism is shown by the fact that a very small area of acid secreting mucosa can elaborate a large quantity of acid, as demonstrated experimentally by Shapiro and Berg That is, the osyntic cells, if they secrete at all, will secrete maximally as determined by simple osmotic considerations There is no evidence to implicate the vasomotor nerves as a direct factor in the control of gastric acidity The gastric mucosa can secrete acid provided it has a blood supply, and all conditions effective in stimulating gastric secretion involve an increased blood supply It is certain that the vagi are not an essential pathway for the secretory impulse since the vagotomized stomach or stomach pouch secretes acid in response to histamine and local mechanical and chemical stimuli

Two important factors in the production, persistence and recurrence of peptic ulcers are the presence of hydrochloric acid in the stomach, increasing in response to psychic influences and increase in tone of the stomach wall to the extent of spasm Dragstedt and others have demonstrated that if both vagus nerves are resected either just above the

it induces secretion of HCL Removal of the pyloric part of the stomach has been found to be an effective method of treatment in cases of peptic ulcer Among its desirable effects is a permanent reduction of gastric acidity which is often excessive in this condition, this effect has been ascribed by some to interference with the "gastrin" mechanism by removal of the tissue which is supposed normally to produce the hormone If the proximal portion of the stomach is removed in peptic ulcer but the ulcer bed in the pylorous is left behind, there will be a higher percentage of recurrence of ulceration in the newly formed stoma than if the pyloric portion containing the ulcer is removed also

The existence of "gastrin" was assumed on the basis of experimental work which demonstrated that an HCL extract of pyloric mucosa when injected intravenously induced gastric secretion However, it has been shown that the substance is not specific, for it also induces pancreatic secretion, and besides, extracts of other tissues produce similar effects

Perhaps histamine is the active principal of the extract, for histamine or extracts of gastric mucosa containing a histamine-like substance injected parenterally are known to cause a profuse flow of gastric juice It is the most potent excitant of acid gastric secretion known and is used commonly in testing gastric function In any case it is highly doubtful that there is any specific "gastrin" mechanism under normal physiological conditions The data at present available do not afford adequate theoretical support for pyloric resection for the purpose of reducing gastric acidity, though it is well established from clinical observation that the operation often produces this effect

That duodenal or jejunal regurgitation plays an important part in reduction of acidity after either resection of the stomach or gastro-enterostomy is generally recognized In cases in which approximately half of the stomach has been resected, Comfort and Osterberg found that whenever bile was present in the gastric secretion the concentration of free acid (and of total chloride) was lower and the concentration of base was higher than when bile was absent In the absence of regurgitation of bile the degree of free acidity was not materially affected in these cases These observers conclude that the elimination of a hormonal or humoral influence of the antral part of the stomach is not indicated by their findings

Fundusectomy for the direct ablation of the acid secreting glands of the stomach does not lower gastric acidity permanently in dogs, according to Seely and Zollinger They found that there was a return of free acid and total acidity to normal in eight months after the operation Zollinger states that the length of time required for this return of

TABLE IX

ANALYSIS OF GASTROSTOMY DIET (FROM FRANSEEN)

Ingredient	*Quantity*	*Foodstuff*			*Minerals*			*Calories*	*Vitamins*				
		Carbohydrate Gm	*Protein Gm*	*Fat Gm*	*Calcium Gm*	*Phosphorus Gm*	*Iron Gm*		*A*	*B*	*C*	*D*	*C*
Milk	840 Gm	42	28	34	1.01	0.78	0.002	585	+++	+++	+	++	+++
Corn syrup (dark)	440 Gm.	324	1	0	—	—	—	1300	0	0	0	0	0
Oatmeal	15 Gm.	10	2	1	0.01	0.06	0.001	55	++	++++	0	0	++
Eggs	250 Gm	0	34	27	0.17	0.45	0.008	380	++++	+++	0	+++	+++
Butter	60 Gm	0	1	51	0.01	0.01	0.000	465	++++	0	0	+++	0
Strained spinach	120 Gm	4	2	1	0.08	0.08	0.003	30	+++	++	+++	0	+++
Scraped beef	30 Gm	0	6	2	0.00	0.02	0.001	40	++	+++	++	++	+++
Orange or grape fruit juice (or)	180 Gm	18	0	0	0.05	0.03	0.000	70	++	+++	++++	0	++
Tomato juice	180 Gm.	7	2	1	0.01	0.03	0.001	45	+++	+++	++++	0	++
Halibut liver oil	10 drops	—	—	—	—	—	—	—	++++	—	—	++++	—
Brewers yeast	10 Gm	4	5	0	0.00	0.16	0.013	35	—	++++	—	—	++++
Ferric ammonium citrate	2 Gm	—	—	—	—	—	0.238	—					
Table salt	6 Gm.	—	—	—	—	—	—	—					
Totals		402	79	116	1.33	1.59	0.266	2960					
Percentage of total calories		54%	11%	35%									

diaphragm, through a thoracic approach, or just below it through an abdominal incision, the nervous phase of gastric secretion is abolished and the total amount of gastric juice produced is markedly decreased The amount of hydrochloric acid excreted at night is greatly diminished The effect of psychic influences is reduced although the secretory response to the entrance of food into the stomach is not altered The tone of the stomach wall is decreased and muscular spasm is much diminished As Dragstedt has expressed it, "It appears clear that this operation, as we have described it, abolishes permanently the nervous phase of gastric secretion and likewise removes the augmenting influence of the vagus nerves on the tonus and mobility of the stomach and small intestines " Following vagotomy the parenteral administration of insulin is not followed by an increase in gastric hydrochloric acid Therefore, the completeness of vagus resection can be measured by administering insulin before and after operation and determining the gastric acidity

Vagus resection is not indicated in the treatment of gastric ulcers because, although the symptoms may be relieved, malignant degeneration in the ulcer may be overlooked Because of its effect upon tone of the stomach wall, the operation is contraindicated in the presence of pyloric obstruction unless it is combined with gastroenterostomy

Friedman, Pincus, *et al*, in 1944 demonstrated that under certain conditions the introduction of acid into the small intestine provokes the secretion of pepsin from the stomach This reaction is absent following the administration of histamine

With regard to the secretion of mucus and pepsin, the "organic" secretions of the gastric mucosa, however, the regulatory influence of nerve impulses, both excitatory and inhibitory, is important There is good evidence that the organic part of the gastric juice is secreted as an alkaline, chloride-rich fluid, it is believed by some to play the major role in the neutralization of the acid secreted by the parietal oxyntic cells "Actual" gastric acidity represents the admixture of the hydrochloric acid secreted by the parietal cells with the alkalinizing secretions of mucus and pepsin

Osseous Atrophy in Hypoacidity In a number of cases of fractured bones in which there was excessive osseous atrophy with delayed calcification at the sites of fracture, Cornell, *et al*, observed reduced gastric acidity and decrease in the volume of gastric secretion Treatment by the administration of hydrochloric acid (4 to 8 cubic centimeters of 10 per cent solution three times a day) was found to increase the absorption of calcium and to promote calcification, of the bone

GASTROSTOMY FEEDING

In the selection of a suitable diet for gastrostomy feeding, the stomach may be considered as an essentially normal organ in most cases The only barrier to the administration of the ordinary hospital or home diet is the size of the lumen of the tube, the diet chosen therefore, although fluid in consistency, should approximate the normal diet as far as possible with regard to the body's requirements for energy (calories), fluids, mineral and vitamins

Franseen describes a gastrostomy diet which has proved adequate and which when properly prepared and administered overcomes a number of difficulties associated with gastrostomy feeding Lactose, so commonly used in gastrostomy feeding, has a marked tendency to cause diarrhea and flatulence, and Koehler and Allen have found that from 40 to 50 per cent may be lost for this reason Corn syrup was found by Franseen to be a very satisfactory substitute for lactose The use of peptonized milk, though common, is unnecessary, whole milk is a satisfactory liquid vehicle for the diet As suggested by Watson butter is used as the supplementary source of fat in lieu of cream Cooked eggs are more digestible than raw eggs and soft poached eggs pushed through a strainer are recommended. Beef scrapings are given as an additional source of animal protein Vegetable purees, conveniently obtained in the canned preparations marketed for infant feeding, provide a small amount of roughage in the diet.

Though the whole day's feeding is prepared at one time, one special feeding is retained for the administration of the scraped beef, fruit juice and iron as these ingredients if added to the whole mixture may impair its consistency or favor bacteriological changes

The feeding mixture is of sufficiently smooth texture so that it can be given through a catheter of small caliber Supplementary parenteral fluids are required during the first three days to maintain an adequate fluid intake On the first day after operation, the patient is already receiving 1,165 calories and the caloric value then advances rapidly each day, the full diet mixture being given by the 8th day It has been found that night feedings are not necessary, and that individual feedings do not have to exceed 11 ounces (350 cubic centimeters), larger feedings may cause leakage about the tube or abdominal distress even though the diet mixture is administered slowly

W S McCune, M D

TABLE X

GASTROSTOMY DIET (FORM FRANSEEN)

Days	*Hours of Feeding*	*Interval Between Feedings*	*Number of Feedings*	*Formula at Each Feeding*	*Total Formula*	*Water at Each Feeding*	*Milk*	*Corn Syrup*	*Supplement*	*Total Daily Fluids*	*Total Daily Calories*
Day of operation	None	—	None	—	—	—	—	—	2,000 cc 10% dextrose intravenously	67 oz	820
1st day after operation	7 A M to 10 P M	1 hr	16	1 oz	16 oz	½ oz	14 oz	2 oz	1,500 cc 10% dextrose intravenously	66 oz	1165
2d day after operation	7 A M to 10 P M	1 hr	16	2 oz	32 oz	1 oz	26 oz	6 oz	750 cc 10% dextrose intravenously	73 oz	1630
3d day after operation	7 A M to 10 P M	1 hr	16	3 oz	48 oz	1 oz	40 oz	8 oz	—	64 oz	1875
4th day after operation	7 A M to 10 P M	1½ hr	11	4 oz	44 oz	1 oz	31 oz	8 oz	2 eggs, 1 oz butter	55 oz	2045
5th day after operation	7 A M to 10 P M	1½ hr	11	5 oz	55 oz	1 oz	37 oz	8 oz	4 eggs, 2 oz butter	66 oz	2530
6th day after operation	7 A M to 9 P M	2 hr	8	6 oz	48 oz	1 oz	30 oz	8 oz	4 eggs, 2 oz butter	56 oz	2385
7th day after operation	7 A M to 9 P M	2 hr	8	7 oz	56 oz	1 oz	38 oz	8 oz	4 eggs, 2 oz butter	64 oz	2550
8th day after operation	8 A M to 8 P M	2 hr	7	10 oz	60 oz	1 oz	32 oz	8 oz	Full diet	77 oz	3020

When a segment of the intestine is reversed by surgical operation, waves of peristalsis continue to pass over the reversed segment in the same direction as before, that is they move toward the duodenum after the operation. Partial obstruction occurs at the upper end of the segment The conception that appropriate stimulation of the gut at any point induces contraction just above and relaxation just below the affected region is referred to as the "law of the intestine" The segmentation movements are thought to occur in response to local distention of the bowel by its contents, being mediated probably through the local nerve net

When a Roux "Y" type of anastomosis is performed in the jejunum of a dog, regurgitation can occur for a distance of 10 inches in the anti peristaltic limb of the "Y" Therefore, when a Roux "Y" type of anastomosis is performed for drainage of bile in common duct injuries, etc, judging by animal experimentation, the optimum length for the anti peristaltic limb is 12 inches An enteroenterostomy between loops of jejunum does not short-circuit these loops and does not divert all of the intestinal streams even when the limbs of the loops are 24 inches in length (Pearse, Radakovich and Cogbill, 1949)

Function of Extrinsic Nerve Supply In 1944 it was demonstrated by Van Liere, Northrop, and Stickney that intramuscular injection of ergotamine increases the motility of the small intestine 27 per cent and prostigmine, 38 per cent and atropine decreases the motility 36 per cent and ephedrine, 35 per cent Cocaine had no appreciable effect on the motility of the small intestine Thus the influence of agents affecting the autonomic nervous system on the motility of the small intestine is similar to that of the parasympathetic and sympathetic nerves respectively However, the extrinsic nerve supply apparently serves the function merely of correlating intestinal activity with events in other parts of the alimentary system and elsewhere in the body Though the vagus is the "motor" nerve it can under certain conditions produce an inhibitory effect on the intestine The sympathetic, though predominantly inhibitory appears under certain conditions to exert a motor influence upon the intestine However, the two nerve supplies are in opposition to each other and when the function of one is eliminated the characteristic activity of the other usually becomes more conspicuous in the behavior of the bowel

Sometimes the net effect upon intestinal motility of interrupting one or the other extrinsic nerve supply is hardly appreciable In this connection the marked autonomy which the bowel has by virtue of its smooth muscle and its intrinsic nerve nets should be borne in mind and

Chapter IX

THE INTESTINES

THE SMALL INTESTINE

MOTILITY OF THE SMALL INTESTINE

Material which has been passed into the first portion of the duodenum is retained there until its acidity is neutralized and is then carried rapidly to the jejunum There is some antiperistalsis in the duodenal cap normally Slow peristaltic waves pass down the small intestine as a whole at intervals varying from a few seconds to a few minutes It takes about one second for a wave to pass any given point By means of these waves the chyme is moved along so as to reach the cecum about 3½ hours after it leaves the stomach Segmentation movements of the small intestine occur, churning the chyme, mixing it intimately with the digestive secretions and exposing it to the absorptive surface of the mucosa The rate of rhythmic segmentation of the intestine is progressively slower in successively lower levels of the bowel It is about 17 to 21 per minute in the duodenum and about 10 to 12 per minute in the ileum The amplitude of contraction, on the contrary, is only about ⅓ as great in the duodenum as in the ileum Dragstedt has shown that in the upper part of the small intestine of the dog, obstruction will result from an amount of pressure that in the lower ileum will not produce obstruction,

Nervous Control of Small Intestine Motility: The means by which the movements of the intestine are regulated are not fully known The vagi increase the tone and motility of the small bowel, and the sympathetic nerves have the reverse effect However, even after both the vagus and the sympathetic nerve supplies have been divided, practically normal peristalsis continues Portions of gut excised from the body exhibit rhythmic movements Hence the normal intestinal movements are probably controlled by means of local mechanical and chemical stimuli affecting the mucosa and causing contraction above and relaxation below the site of stimulation, Auerbach's plexus probably conveying the impulses which bring about this co-ordinated response

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Sometimes the net effect upon intestinal motility of interrupting one or the other extrinsic nerve supply is hardly appreciable In this connection the marked autonomy which the bowel has by virtue of its smooth muscle and its intrinsic nerve nets should be borne in mind and

also the fact that the function of the extrinsic nerves is not to supply the intestine with a certain degree of motor power from without, but rather to adapt the motility possessed by the bowel itself to conditions and needs in other parts of the organism

Spinal Anesthesia and Intestinal Motility Spinal anesthesia reduces or removes entirely the action of the sympathetic nerve supply upon the intestine and thereby favors intestinal motility under the unopposed influence of the vagus. The extent to which the movement of the gut is actually increased depends upon the conditions obtained at the time the spinal anesthesia is induced, that is, whether the sympathetic is acting strongly or weakly, whether the vagus is acting strongly or weakly and whether the bowel itself is just then disposed to activity or quiescence by reason of the obscure factors which determine its inherent autonomy The effect of sectioning of the vagi, which is often done in connection with gastric operations, depends upon this same group of conditions. In either case the result is nearly always temporary, the intrinsic autonomy of the bowel quickly regains predominance and obliterates the positive or negative motor imbalance which loss of the sympathetic or vagus influence tends to permit Exceptionally there appears to be permanent overactivity of one of the nerve supplies, congenital in origin In these instances disturbances of bowel function may be permanently relieved after section of the overacting nerve supply In 1948, Dennis and his co-workers reported the results of vagotomy in 11 patients suffering from idiopathic ulcerative colitis By means of this procedure, the time required for passage of barium through the small intestine was increased to 3½ hours before operation to 7½ hours post-operatively The passage of barium through the colon was increased from 3 1 hours preoperatively to 11 3 hours after operation The results were most marked and most prompt in cases in which there was not great loss of distensibility of the colic wall, Vagotomy reduced the mucosal vascular response to intense emotion and relieved enteric spasm

Effects of Heat and Cold on Gastro-intestinal Motility Bisgard and Nye studied the effects of heat and cold on gastro-intestinal motor activity by means of continuous kymographic recordings of the variations in pressure within the stomach and bowel, rubber balloons being introduced on Miller-Abbott tubes into these organs for that purpose They found that hot packs applied to the abdominal wall had an inhibitory effect upon gastric and intestinal motor activity, whereas hot water administered by mouth (six ounces) had a pronounced motor effect on the entire gastro-intestinal tract, causing increase in both tonus

and peristalsis Ice packs applied to the abdominal wall caused vigorous motor responses in the stomach and intestines, whereas iced water (six ounces) given by mouth had a slight but definite inhibitory effect upon the stomach and bowel External hot applications did not alter the acidity of the gastric contents, while external cold applications caused "big increases" in both free and total acids Simply immersing the hands in iced water for a few minutes caused a rise in gastric acidity similar to that resulting from the subcutaneous injection of histamine The ingestion of iced water diminished the secretion of acids by the stomach

From these findings it would seem, as Bisgard and Nye point out, that if inflammatory lesions such as appendicitis and peritonitis are benefited by inhibition and rest of the gastro-intestinal tract, then hot applications and not ice bags are indicated In these conditions the motor effect of the cold applications which are commonly employed may actually be deleterious In the treatment of distention it would seem, from these observations, that ice packs would be more effective than hot applications for expelling gas Also, in post-operative patients cold water by mouth would cause less disturbance than warm water However, the onward movement of gastric and intestinal contents involves the proper integration of motor activity in the adjacent segments of the stomach and bowel and in the sphincters Peristalsis, regardless of its vigor, is ineffectual when disorganized As a given segment contracts, if the adjoining distal segment fails to relax, the intestinal contents fail to move normally and cramp-like pains may result Under these circumstances, as Bisgard and Nye remark, the increased peristaltic activity resulting from cold applications might serve only to aggravate the disturbance and increase the patient's discomfort. Hot compresses,' on the contrary, by their inhibitory effect, may be more conducive to coordinated motility of the bowel Certainly clinical observation proves that hot applications are definitely more effective than cold ones for the relief of colicky pains. However, the Bisgard and Nye believe, from clinical evidence, that cold applications are more effective in relieving distention

Chemical Control of Small Intestine Motility *Hormone Control* Hormone control of intestinal motility is undoubtedly of great importance A thyroid influence is indicated by the frequent occurrence of diarrhea in exophthalmic goiter and constipation in myxoedema. The posturitary hormone, vasopressin (pitressin) promotes contraction and movement of the intestine by direct action on the smooth muscle The relative importance of this substance in the control of normal intestinal

motility is not known Reduction of serum protein concentration has been shown by Barden, *et al*, to be associated with a marked retardation of the movement of the barium meal in the small intestine of the dog This impairment of motility can be corrected by restoring the serum protein to normal

Effects of Drugs and of Sodium Chloride Prostigmine, a synthetic compound resembling the parasympathetic stimulant physostigmine (eserine), is reported by Harger and Wilkey to be a satisfactory agent for the prevention or treatment of distention and paralytic ileus, with a low incidence of by-effects in the 175 clinical cases in whch it was used by them The effect of morphine on the intestine seems to vary with conditions, but according to Paine, *et al*, the drug uniformly enhances both the tone and the peristaltic activity of the intestine, both normal and obstructed The constipating action is attributed to increased tone of the sphincters and depression of the afferent limb of the defecating reflex Paine, *et al*, concluded from their study of postoperative patients that morphine neither prevents nor relieves abdominal distention nor is an important factor in producing distention

Forster, by means of special apparatus, recorded separately the motor activity of the circular and longitudinal muscle of the lower third of the ileum in a case of bowel exteriorization with ileostomy in an otherwise healthy man Continuous kymographic tracings were taken Two types of activity were observed, propulsive and non-propulsive activity (peristalsis), but the longitudinal muscle contractions began first, followed after one to one and one-half minutes by the onset of circular muscle contraction, also the longitudinal muscle contraction continued after the circular muscle contraction had ceased Such peristaltic waves had an average duration of one to six minutes and occurred one to six times in 30 minutes. The non-propulsive (mixing) activity consisted of alternate phases of contraction and relaxation lasting six to 12 seconds each, nine to 150 complete waves occurring in a 30-minute period.

King and Robinson in 1945 based upon reactions of intact and isolated sections of small and large intestine to acetyl choline and adrenalin with or without nicotine, atropine or ergotomine, concluded that the muscularis mucosa is inervated by both cholinergic and adrenergic motor nerves Rhythmic movements of the muscularis mucosa appeared to be basically myogenic, but could be initiated or augmented through its nervous mechanism The muscularis mucosa activities were shown to affect transport and disposition of material in the GI tract entirely aside from the (pump) activity of villi which

had previously been described as facilitating flow of lymph from the intestine These workers have been unable to find evidence of such a pumping action

Morphine sulphate, grain ⅛ completely suppressed the peristaltic wave and increased the frequency of the mixing wave, a larger dose decreased the frequency of the mixing wave and increased the tone of both muscle coats Atropine sulphate, grain 1/150, decreased the fre quency of both the peristaltic and mixing waves, and a larger dose suppressed the former completely and the latter nearly completely

Observations on intestinal peristalsis through a cellophane abdominal window in rabbits were made by Schnohr Cooling caused cessation of peristalsis, as did injection of atropine, intraspinal anesthesia and anoxemia or increased CO_2 of the blood In the last two conditions marked contraction of the arteries of the intestine occurred simultane ously with the cessation of movement Injections of pituitary extract caused abnormally violent uncoordinated contractions of short dura tion. Intravenous injections of hypertonic solutions of sodium chloride (7 to 25 per cent) caused peristalsis of normal type and of long duration in a paralyzed bowel These injections also had a marked diuretic effect and accelerated the absorption of peritoneal exudates Orr, *et al*, con firmed the stimulating effect of sodium chloride solutions on peristalsis in experimental animals

Feigen and Campbell have demonstrated that surviving intestinal strips react to antigens and non specific substances such as histamine and acetyl choline only when these agents are applied to the peritoneal surface of the intestine. When applied to the mucosal surfaces they have no effect presumably because of the thickness of the mucosal layer The response to substances applied to the peritoneal surface is extremely rapid which makes it appear that the antigenic substances must reach the intestinal muscle by way of the circulation. These experiments were carried out on a guinea pig When conjugated bile acids, desoxycholic acid and cholic acid, choline and also choline salts of these bile acids are applied to the internal surface of the small and large isolated intestine of the guinea pig in low doses, stimulation of the rhythmic movements is produced With higher doses the tonus increases and tends to counteract the wave movements The rate is slowed and the amplitude of the waves decreases Curare in therapeutic amounts causes relaxation of smooth muscle of the small intestine (Gross, Cullen) When hemorrhage of about 20 per cent of the total estimated blood volume was produced in experimental animals, immediate cessation of intestinal activity occurred followed by immediate recovery upon re-

placing the withdrawn blood, by reinjection of the cells suspended in Ringer's solution Depletion of plasma proteins by repeated plasma phoresis brought about a definite decrease in intestinal activity with delay in the appearance of feeding reactions On replacing plasma proteins, intestinal motility returned to the control state before proteins had risen to a normal level (Wakin and Mason, 1945) Van Liere, Northrop and Stickney had obtained similar depression in the height and number of contractions of the smooth muscle of the colon following hemorrhage amounting to 1 5 per cent of the body weight of dogs In a group of dogs subjected to hemorrhage equivalent to 3 per cent of their body weight, however, it was observed that intestinal motility of the small bowel was increased possibly because the hemorrhage stimulated parasympathetic nerves more than sympathetic Under the influence of anoxia (partial pressures of oxygen from 80 to 43 millimeters of mercury) the small intestine was unaffected The height of contractions of both the circular and longitudinal muscles of the colon was decreased by anoxia, the first change in activity occurring at partial pressures of oxygen from 110 to 94 millimeters of mercury This corresponds with an approximate altitude of from 10,000 to 14,000 feet Cocaine prevents the acceleration of small intestinal motility under the influence of hemorrhage equal to 3 per cent of body weight Thus cocaine apparently has a synergistic action with anoxic anoxia stimulating sympathetic nerves and decreasing intestinal motility When anemic and anoxic anoxia are combined, the anoxic anoxia apparently stimulates sympathetic fibers, and acceleration of propulsion in a small intestine ordinarily produced by anemic anoxia alone is prevented

Use of Sodium Chloride in Ileus. Keusenhoff reports beneficial results in clinical cases of postoperative ileus from the intravenous injection of 10 to 20 cubic centimeters of a 10 per cent solution of sodium chloride, in some cases, in addition he gave by rectum 125 to 150 cubic centimeters of a 20 per cent solution of sodium chloride Genkin and Milyavskaya found enemata of 100 cubic centimeters of 15 per cent sodium chloride solution effective in the treatment of postoperative ileus, even after other measures failed The response was so consistently good that they preferred this treatment to the intravenous injection of sodium chloride They consider the procedure valuable as an aid in differentiating between functional and mechanical ileus That hypochloremia depresses peristalsis was shown by Eitel and Loesser by means of experiments on excised segments of the intestine of animals.

Effects of Dextrose on Peristalsis Bulatao and Carlson reported that in dogs intravenous injections of 50 per cent dextrose caused an inhibi-

tion of gastric hunger contractions This conclusion has frequently been extended by inference to other portions of the alimentary canal Quigley and Highstone, in a study of the intestinal propulsive rate by the bolus method, found that intravenous injections of dextrose solutions (5, 10 and 25 per cent) usually produce no pronounced change in the rate at which a bolus traverses a loop of the dog's jejunum, though with the hypertonic solutions propulsion may be somewhat augmented A delay in propulsion appears to be an atypical response

After gastroenterostomy the fat content of the feces generally increases This is due to excessively rapid passage of the chyme through the jejunum so that there is not enough time for absorption of the fat In some patients this chronic loss of fat seems to be the cause of emaciation and fatigue However, true fatty feces and fatty diarrhea after gastroenterostomy indicate a gastrojejunocolic fistula

Intestinal Distention *Influence of Distention on Intestinal Secretion* Herrin (1935) observed that as a result of distention of the intestine, which stimulates the secretion of true intestinal juice, the chloride concentration of the intestinal juice decreases but it still remains higher than that of the blood serum, even though the latter be greatly reduced A marked lowering of plasma chloride concentration therefore, is no protection against further losses of chloride Similarly, in distention there is an enormous increase in the concentration of bicarbonate in the intestinal juice, even though the serum bicarbonate is diminished It is apparent, then, that the intestinal glands secrete chloride and bicarbonate quite independently of the concentrations of these ions in the blood Ammonia is not secreted by the intestine normally but is secreted in large amounts in distention Herrin found that distention accelerates the rate of secretion of intestinal juice by from 170 to 567 per cent

Treatment by Oxygen Inhalation Gas is normally present throughout the intestinal tract, but in adults it is visualized normally only in the stomach and colon on X ray examination, the intermixture of gas and fluid is so intimate in the small intestine that gas is not visible on the roentgenogram unless there is stasis Blair, *et al*, have measured the volume of gas in the digestive tract by determining its change in volume during compression by maximal expiratory effort The average content of gas in the intestinal tract of male subjects is about 1 liter Gas expelled varied from 12 cubic centimeters in 24 hours to 2,600 cubic centimeters in different subjects on different diets They found that the volume of flatus expelled was largely dependent upon the motility of the digestive tract When the motility is low a small volume of gas of

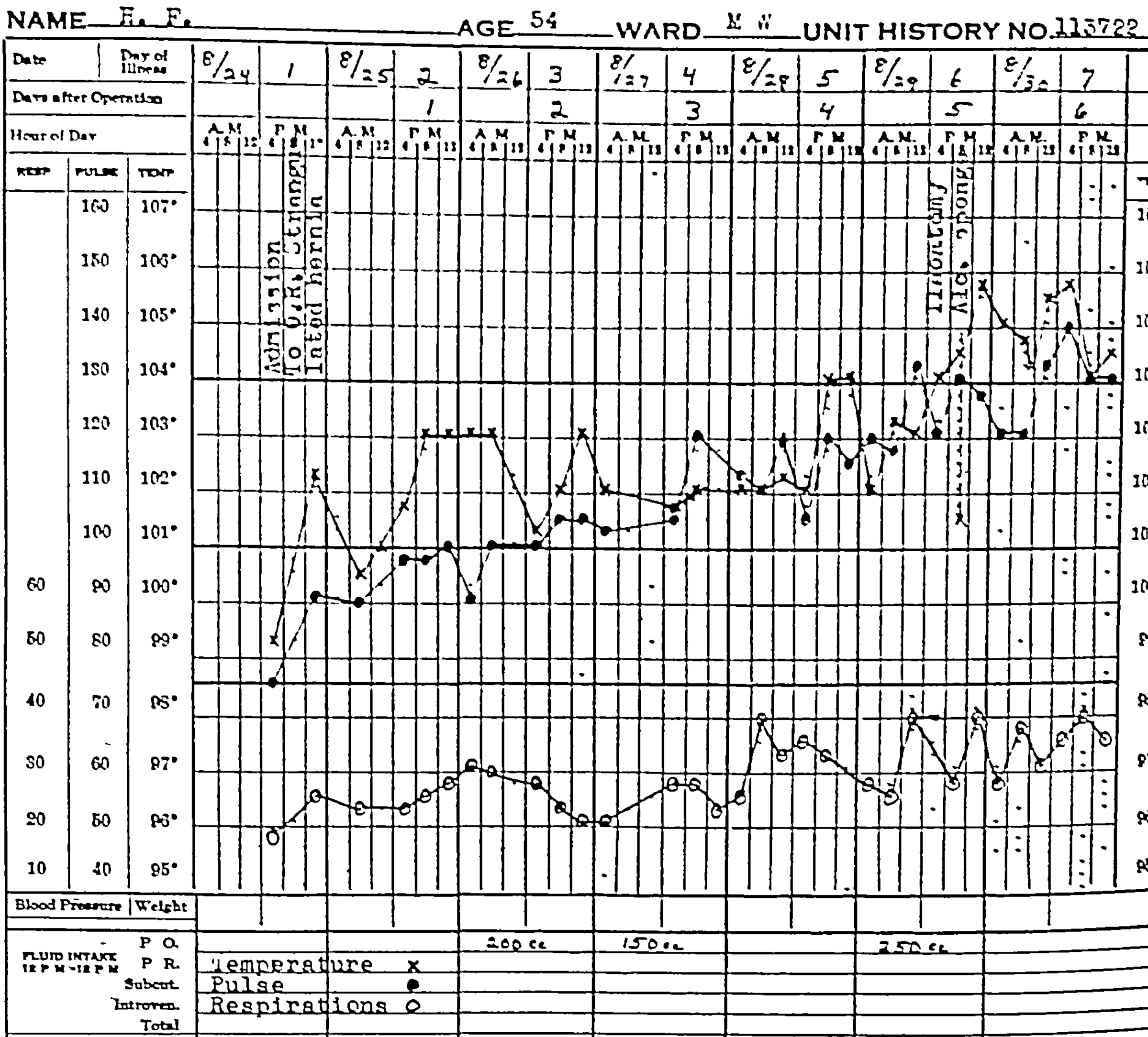


FIG 10 Rising temperature and pulse rate in a patient who developed paralytic ileus following herniorrhaphy for repair of a strangulated hernia (x—temperature pulse rate o—respirations)

high nitrogen concentration but low nitrogen content is egested. Thus, even though swallowed nitrogen is absorbed slowly it may be absorbed almost completely The source of gas in postoperative distention and in intestinal obstruction is largely swallowed air. McIver *et al*, found that the chief constituents were nitrogen and hydrogen They showed experimentally that when the obstructed small intestine was inflated with these gases, a substantial reduction of the gas volume could be accomplished by means of inhalations of pure oxygen The oxygen acts by preventing the entrance of atmospheric nitrogen into the lungs, in consequence the blood and tissues pour their nitrogen into the lungs losing as much as 60 per cent of their nitrogen content in one hour

Fine, *et al* (1936), extended these experiments and recommended treatment of intestinal distention by the inhalation of a high concentra-

tion of oxygen (95 per cent). They found the treatment ineffective for distention of the stomach, possibly because of the small area available for gas exchange, 70 per cent oxygen was found to have no beneficial effect In animals the administration of over 70 per cent oxygen for a long time eventually caused pulmonary edema

In clinical cases of ileus, Fine, *et al* (1938), found that for four or five hours there was no appreciable decrease in abdominal measurements, but that after that length of time the abdomen had become softer (Figures 19 and 20) They explain that girth measurements do not accurately reflect the degree of intestinal distention when the abdomen is tense, for as the abdominal wall relaxes, the displaced diaphragm and liver return to their normal positions, and so, for a time, the girth may actually increase Ninety five per cent oxygen was administered to patients for as long as 35 hours, with only half hour rest periods about every four hours, without toxic effects Rosenfeld and Fine showed that

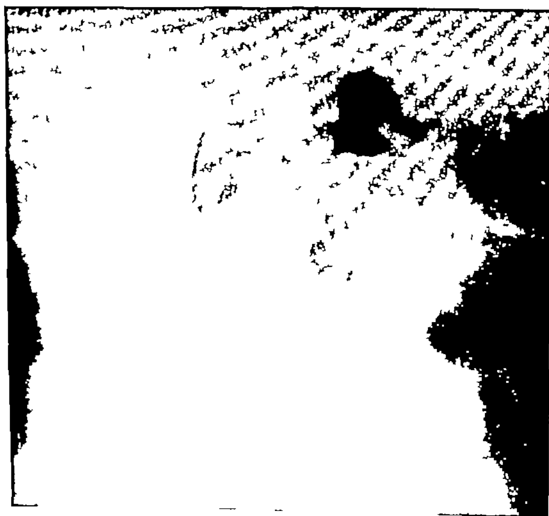


Fig 20 Dilatation of small and large intestine in paralytic ileus

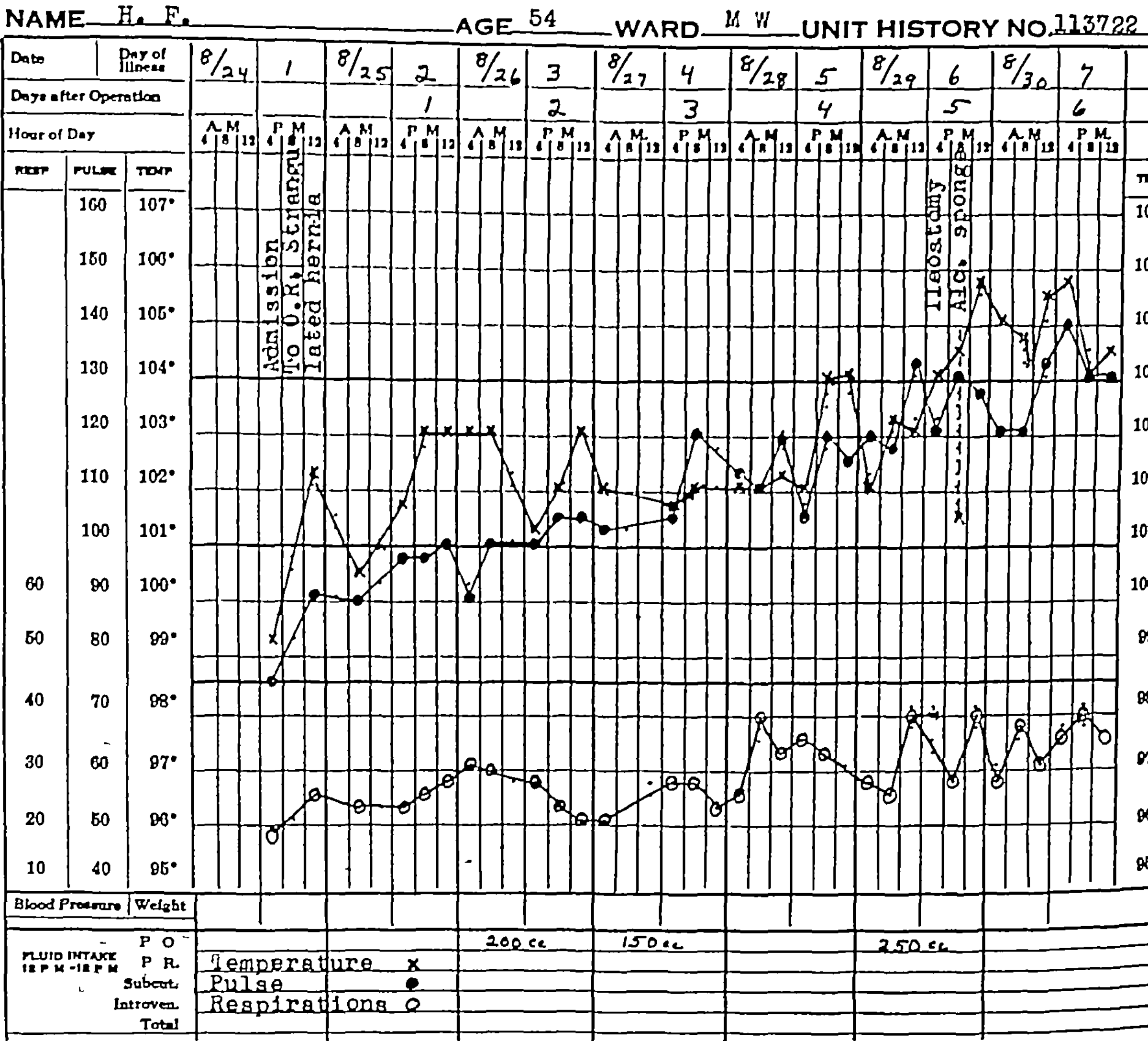


FIG 19 Rising temperature and pulse rate in a patient who developed paralytic ileus followin herniorrhaphy for repair of a strangulated hernia (x—temperature, pulse rate, o—respirations

high nitrogen concentration but low nitrogen content is egested. Thus, even though swallowed nitrogen is absorbed slowly it may be absorbed almost completely The source of gas in postoperative distention and in intestinal obstruction is largely swallowed air. McIver, *et al*, found that the chief constituents were nitrogen and hydrogen They showed experimentally that when the obstructed small intestine was inflated with these gases, a substantial reduction of the gas volume could be accomplished by means of inhalations of pure oxygen The oxygen acts by preventing the entrance of atmospheric nitrogen into the lungs, in consequence the blood and tissues pour their nitrogen into the lungs, losing as much as 60 per cent of their nitrogen content in one hour

Fine, *et al* (1936), extended these experiments and recommended treatment of intestinal distention by the inhalation of a high concentra-



FIG 21 (b) Same Tube in lower jejunum of ileum.

due to coronary narrowing through vagal pathways In animals with small abdominal areas circulatory failure and death occurs earlier with a given intra abdominal pressure (Booker, *et al* 1947)

Treatment of Intestinal Distention by Duodenal Suction As the chief source of postoperative distention is known to be swallowed air, Wangensteen introduced a method for obviating its occurrence at the source by means of constant suction with a duodenal tube The absences of sphincters between the pylorus and the cecum makes the suction applied

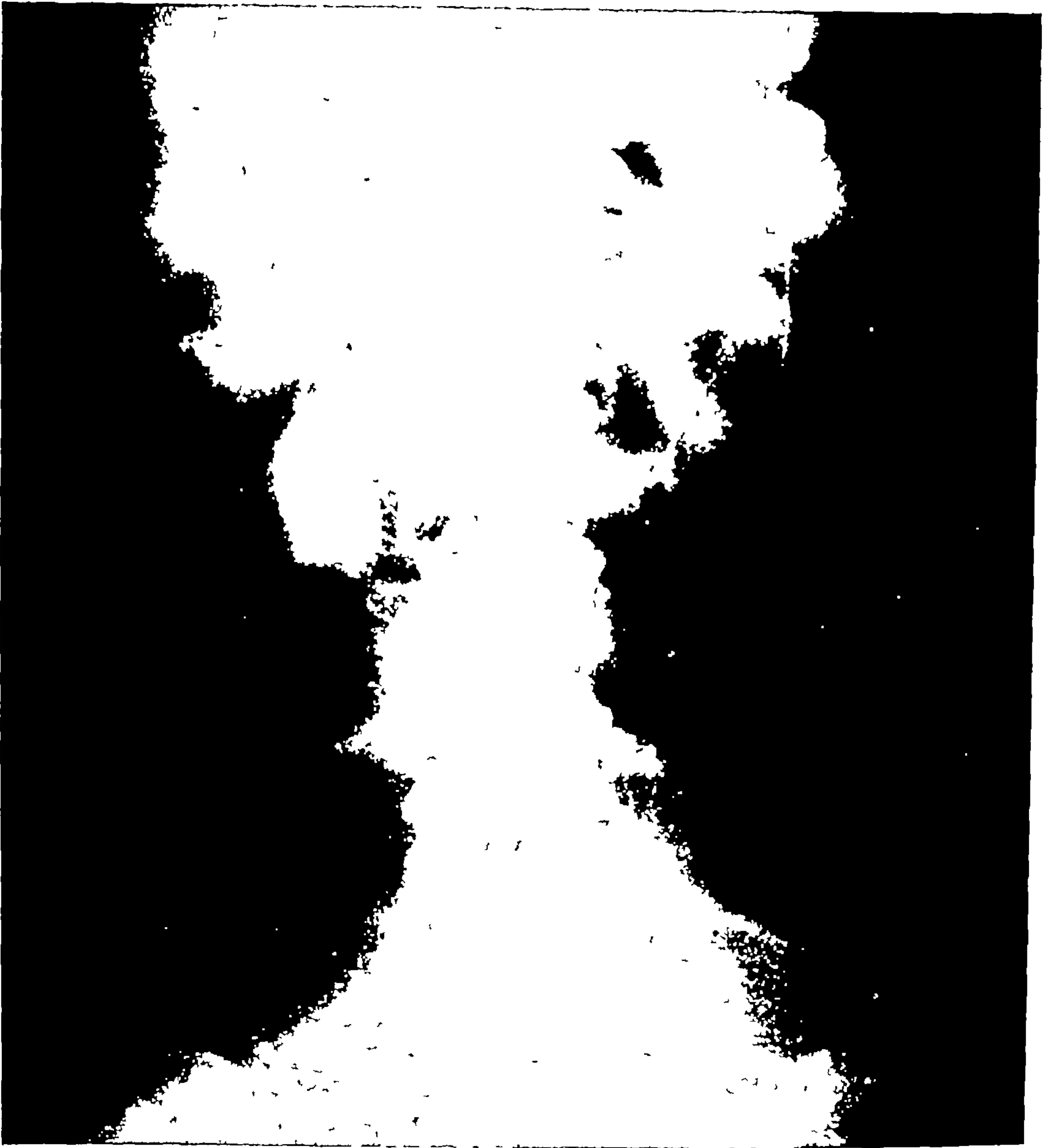


FIG 21 (a) Use of Miller-Abbott tube in peritonitis with ileus due to acute purulent salpingitis (a) Tube entering duodenum

in experimental obstruction of the small intestine in cats, with an initial intraluminal pressure of 800 mm H_2O, those animals which were left in atmospheric air all died in less than 11 7 hours with a fall of intraluminal pressure to only 433 mm H_2O on the average, whereas those animals placed in oxygen all lived 18 8 hours or longer and the intraluminal pressure fell to 273 mm H_2O or less in every case, in the majority falling to normal (20 to 40 mm H_2O)

When the intra-abdominal pressure is increased by pneumoperitoneum, or by distending the stomach or intestine, circulatory failure occurs There is suggestive evidence of myocardial damage, possibly



FIG. 22 Huge dilatation of the cecum and ascending colon in a case with an obstructing lesion of the sigmoid showing the effect of a competent ileocecal valve in preventing reflux into the terminal ileum.

an hour The valve opens with each peristaltic wave in the terminal ileum and about a dram of fluid feces together with some gas is allowed to pass into the cecum These waves are rather infrequent ordinarily, but are more frequent immediately after the ingestion of food by reason of a so-called gastro-ileal nerve reflex via the vagus The ileocecal sphincter is able to withstand a pressure of only about 100 millimeters of water from the cecal aspect and is easily overcome by the barium enema administered from a height of about 450 millimeters Under normal conditions it is competent, however, as antiperistalsis in the ascending colon is feeble, In cases of acute obstruction of the large intestine, the ileocolic valve usually remains tightly closed, confining the distention to the colon, even though the pressure within the colon

at one end of the small intestine appreciated to some extent at the other end, even when the content of the bowel is not homogeneous but consists of a mixture of gas and fluid Decompression by suction is not as readily accomplished in the quiescent bowel of postoperative distention as in the active peristalsis present in bowel obstruction Nevertheless, intercepting the oral source for accretion of distention permits time for some readjustment of the relative positions of gas and fluid, facilitating their removal through the tube, and permits advantage to be taken of the process of fluid absorption by the intestinal wall Paine *et al*, from their experience with this nasal suction method concluded that postoperative vomiting is caused chiefly by stasis in the stomach and upper intestinal canal The procedure was found to be of particular benefit following gastric operations It did not have any appreciable effect in controlling "gas pains" or postoperative constipation Distention of the paretic intestine can be more easily prevented by suction than relieved after it becomes established

In 1934 Miller and Abbott developed a double lumen balloon tipped tube for intubation of the small intestine (Figure 21 a & b) In 1938 Abbott and Johnston announced the passage of this tube well down into the lower reaches of the bowel in patients with mechanical obstruction of the small intestine Inflation of the small balloon at the tip of the tube stimulated the intestine to contract upon it and the peristaltic waves resulting moved the balloon and tube down the bowel. Even in cases of paralytic ileus there is enough peristaltic activity remaining to force the balloon down the intestinal tract The chief difficulty is in passing the tip of the balloon through the pyloric sphincter In 1945 Harris recommended the use of mercury in the balloon to draw the tube through the pylorus through the aid of gravity In 1948 McLanahan described a method of localizing the tip of the tube with balloon by listening over the abdomen with a stethoscope while air is forced into and out of the balloon with a syringe A characteristic sound localizes the exact situation of the balloon in the abdomen in the intestine When an intestinal tube is used, the danger of removing fluid and electrolytes from the bowel in excessive amounts must be remembered Such fluid loss must be compensated for by parenteral glucose and saline administration.

The Ileocolic Sphincter · The ileocolic sphincter is closed most of the time, its main function apparently being to prevent too rapid entrance of the ileal contents into the cecum so that there will be more time for digestion and absorption in the small intestine The onward movement of the chyme is thus delayed in the terminal ileum for about

of pancreatic juice into the intestine It is possible that secretin, known to have a controlling influence over the production of pancreatic juice, also acts directly as a stimulus to the secretion of intestinal juice

A hormone mechanism is indicated by the fact that a transplanted loop of intestine exhibits a slight increase of secretion following the ingestion of food The hormone control, however, appears to play a minor part. It is estimated that 3,000 cubic centimeters of intestinal juice is secreted in 24 hours Nearly complete absorption of the nutritive products of digestion occurs in the small intestine

Reaction of Intestinal "Contents" The reaction of the intestinal contents, as distinguished from intestinal secretion, at any given level, depends on the reaction of the chyme as it approaches that level, its rate of movement due to peristalsis and the rate of secretion of neutralizing fluids There occur variations in pH of from 4 to 7 6 in the jejunum, 5 4 to 8 in the ileum and 4 4 to 7 4 in the colon (deBeer, *et al*, 1935) The sensitiveness of the intestinal mucosa to the acid of the gastric juice increases from the duodenum down Mann and Bollman have shown that dietary measures may greatly alter the reaction of the contents of the gastrointestinal tract

Electrolyte Composition of Intestinal Secretion In all the intestinal secretions sodium is the chief inorganic cation The concentrations of the various cations (Na, K, Ca and undetermined) are approximately the same in the secretions of different parts of the intestine The two chief anions, Cl and HCO_3, exhibit marked reciprocal variations, the HCO_3 increases in the lower parts of the intestinal tract, its concentration becoming equal to and sometimes even greater than that of Cl in the terminal ileum and the colon Through isotopic tracer studies Fetcher, Carr, *et al* have demonstrated that the rate of movement of water from the blood stream into the intestine is nearly independent of the osmotic pressure in the intestine Movement of water from the intestine into the blood depends in general in direction and magnitude upon the osmotic activity gradient In the case of solutions near isotonicity, however, absorption may occur although the osmotic activity gradient is zero or negative The rate of chloride movement from the intestine to the blood increases with increase of chloride concentration, but not in a linear proportion Movement of chloride from the blood to the intestine is independent of the chloride concentration in the intestine The rate of sodium movement from the intestine to the blood is greater from isotonic chloride than sulphate solutions although the intestine sodium concentration is higher in the latter case It appears therefore, that the presence of an anion to which the intestinal wall is relatively

attains a high level (Figure 22) Vomiting is often absent in such cases The sphincter is innervated entirely by the sympathetic and remains open permanently when the sympathetic supply is divided in animals The vagus has no detectable influence upon it, the sympathetic apparently controlling both contraction and relaxation Reflex overaction of the ileocecal sphincter is perhaps responsible for the stasis in the terminal ileum shown by x-ray in some cases of chronic constipation and chronic appendicitis

From anatomical studies Wakefield and Friedell found that the degrees of incompetence of the ileocecal valve are associated with demonstrable structure differences of the valve The valve is competent in about 50 per cent of cases In the presence of an obstructive lesion of the distal part of the colon, whether or not the small intestine becomes distended early depends on whether the valve is competent or incompetent If the valve is competent, distention may be confined to the large bowel and there is great danger of gangrene and perforation of the cecum, whereas if the valve is incompetent, the intestinal contents, including gas, will regurgitate through it, relieving the pressure within the colon and making perforation less likely to occur

These authors call attention to the fact that even though the ileocecal valve is competent, it is possible for the small intestine to become *distended in a case of obstruction of the distal part of the colon* This is because of secondary obstruction at the ileocecal valve, the pressure in the cecum becomes so great that the ileum is not powerful enough to force its contents into the cecum, and distention of the small bowel follows In such cases intubation and decompression of the small intestine will produce great relief of symptoms, but without relieving the dangerous distention of the cecum and colon Decompression of the obstructed large bowel by the introduction of the long intestinal tube can be successful only if the tube is inserted beyond the ileocecal valve. Failing this, early surgical treatment is indicated

SECRETION AND ABSORPTION IN THE SMALL INTESTINE

Composition and Control of Secretion The secretion of the small intestine is alkaline in reaction It contains enzymes capable of splitting proteins (eropsin), carbohydrates and fats, also enterokinase, a substance which is necessary for the activation of the protein-splitting enzyme (trypsinogen) of the pancreatic juice Mechanical stimulation of the intestinal mucosa induces secretion, but the secretion formed in response to mechanical stimulation contains very little enzymes

The most effective stimulus for intestinal secretion is the entrance

of the plasma The chloride loss is in some respects more serious than the loss of the fixed base or the bicarbonate because the bodily stores of chloride are less in amount than those of fixed base, and all chloride must be obtained from without whereas bicarbonate can be formed as needed in the body from the carbon dioxide produced in metabolism

Experimentally Herrin found that as a result of loss of intestinal juice, fixed base of the blood decreased on the average about 10 per cent, chloride, 26 per cent and bicarbonate, 20 per cent Loss of cations is not tolerated as well by the organism as loss of anions, for the chloride loss may amount to 26 per cent, yet a 10 per cent reduction in serum base may be more detrimental Deficiency of electrolytes greatly modifies the ability of the tissues to hold water and also other general physiological properties The inorganic pattern of intestinal juice differs from that of the blood plasma in that the chloride and fixed base concentrations are somewhat higher and the bicarbonate somewhat lower than those of plasma, and there is much more acid soluble phosphorus than in plasma

Reports concerning the inorganic pattern of the blood following loss of intestinal contents in intestinal obstruction or in external fistula of the intestine do not agree with one another The conflicting data are due to the fact that the relative amounts of gastric, pancreatic and intestinal secretions lost are not always the same The findings vary most markedly with reference to the bicarbonate content of the blood If the fluid lost is mostly intestinal secretion, which is usually the case, since this has a high bicarbonate content as compared with gastric juice, alkalosis does not occur. The inorganic phosphorus content of the serum increases markedly; also the ester phosphorus of the blood cells, the latter probably represents phosphate retained by base as a substitute for lost chloride The total phosphorus increase amounts to about 60 per cent Serum calcium increases 12 to 28 per cent The increase in calcium is possibly due to changes in the distribution of muscle electrolytes as a consequence of the loss of electrolytes in the intestinal secretion

As Macnaughton states there appear to be some factors contained in the normal digestive juices which contribute markedly to health and to recovery after operation which cannot as yet be replaced by intravenous therapy

The presence of digestive juices in the drainage from ileostomy stomata often causes severe inflammatory reactions in the surrounding skin due to their digestive action Various means of protecting the skin have been devised one suggested by Levy consisting in an aluminum container which fits snugly over the stroma with vaseline gauze against

impermeable impedes movement of cations through the wall There seems to be a forced flow of fluid across the intestinal epithelium in both directions simultaneously The direction and magnitude of transport depends on differences in solute content in the two streams in relative rates of the streams

Clarke, Ivy and Goodman (1948) have demonstrated that resection of mesenteric lymph nodes in dogs does not alter the fat and nitrogen excretion in the feces There is a rapid re-establishment of anatomic and functional continuity of the interrupted mesenteric lymphatics following such lymph node resection In 60 per cent of the dogs there was partial regeneration of the resected nodes Three of four animals studied showed normal values of elementary lipemia six to 12 days after operation Transportation of food materials from the intestinal tract is dependent upon the blood flow through mesenteric vessels Page and Abell (1945), in a microscopic study of mesenteric blood vessels in dogs, observed that after acute hemorrhage resulting in a fall of blood pressure to 30 or to 35 millimeters of mercury for periods of 30 to 45 minutes, mesenteric arteries become constricted from 20 to 60 per cent after removal of 2 5 to 5 5 per cent of body weight of blood Arterioles are constricted to a similar degree and sometimes to a slightly greater extent Often larger veins are also constricted from 12 to 43 per cent Venules do not constrict, they are sometimes dilated At blood pressure levels of 30 millimeters of mercury (3 5 to 5 5 per cent of body weight of blood removed), arterial flow is slow, pulsations sometimes intermittent There is frequent stasis The capillary bed is ischemic for the most part, the intestine being bluish red in contrast to its normal pink color Gaster, Davis, *et al*, in 1949 demonstrated that devascularization of small intestinal loops in rabbits is compatible with life if the loops are up to 7 centimeters in length Removal of blood supply to areas of intestine more than 7 centimeters in length usually causes death from gangrene and perforation The duration of life after devascularization is inversely proportional to the length of intestine deprived of its blood supply

ILEUS AND FISTULA OF THE SMALL INTESTINE

Effects on Body Fluids The inorganic chemical composition of the normal secretion of the small intestine, though differing in some details, is in general very similar to that of the blood plasma Therefore any loss of intestinal secretion from the body represents a loss of the electrolytes from an approximately equal volume of plasma The result is a corresponding reduction in the fixed base, the chloride and the bicarbonate

reduced perhaps only 30 to 40 per cent Under such circumstances the tissues have been drained of their electrolytes to a much greater degree than is indicated by the blood findings Loss of electrolytes may in fact reach the lethal point even when there is practically no change in the serum electrolyte concentration, the hemoglobin and protein concentrations however are increased 25 to 30 per cent in such a case, viscosity is increased 113 to 190 per cent and, more important, the total plasma volume is reduced considerably

Loss of Plasma Volume The shrinkage in plasma volume would appear to be the inevitable serious change which occurs when the electrolyte reserves in the tissue fluids are exhausted and are no longer able to support plasma volume by replacing its lost electrolytes At this stage, since the hemoglobin concentration is above normal, the arterial blood contains an increased amount of oxygen, yet it is not saturated with oxygen as completely as normal blood, probably because the abnormal electrolyte environment renders each unit of hemoglobin less capable of holding oxygen Therefore the net oxygen tension of the blood is reduced, being only about 57 to 65 per cent of normal, this represents a rather severe degree of anoxic anoxemia, which is present despite the excess of hemoglobin in the blood

Fine, *et al* (October, 1940), observed clinically that in small intestinal obstruction, merely decompressing the bowel halted the loss of plasma volume that was taking place, and might even permit the recovery of a substantial fraction of the amount that had been lost Distention of even as little as two feet of the small intestine was found to cause the loss of a significant amount of plasma, whereas distention of the colon failed to do so This difference corresponds well with the marked clinical difference between small and large bowel obstruction These authors are convinced that the decrease in total plasma volume is due to the distention, and not to the obstruction, since it also occurs, they state in severe intestinal distention of functional origin

They noted that the loss of plasma was very great (hematocrit increase of 12 to 25 5 per cent) even in patients who were well hydrated, so dehydration did not seem to be a factor In the normal individual even severe dehydration causes only a moderate increase in hematocrit (7 1 per cent Coller and Maddock) The plasma loss was generally proportional to the degree of the intestinal distention The magnitude of the plasma loss (30 per cent or more of the total plasma volume) seemed to suggest that it was a basic factor in causing death from obstruction

If this is so then even when decompression of the intestine has been

the skin and drains the discharge from the ileostomy through a side tube into a container Dragstedt (1946) has demonstrated the advantage of bringing out a somewhat longer length of ileum and surrounding this with a split-thickness skin graft making it possible to prevent drainage of ileal contents onto the skin.

Blood Potassium in Intestinal Obstruction. A rise in blood potassium to levels known to be lethal was observed in cats with acute intestinal obstruction (all levels) by Scudder *et al* The potassium content of the intestinal loops, of the peritoneal fluid and of the vomitus was much greater than that of the blood Blood density usually rose parallel to the rise of potassium These observers ascribed the rise of potassium to dehydration, tissue breakdown, bacterial toxins and consequent adrenal and renal dysfunction reducing potassium elimination They suggested that potassium is the dialyzable toxic factor which many have sought as the lethal agent in intestinal obstruction Their findings were confirmed by Cutler and Pijoan A more likely cause of death in intestinal obstruction, however, as suggested by Wangensteen is the absorption of intestinal contents and toxic substances through devitalized intestinal wall In complete intestinal fistulae in cats (four different levels tried) a similar rise of blood potassium was reported by Scudder and Zwemer However, Bisgard, *et al*, failed to find any change in serum potassium in high intestinal obstruction Moreover, in man, Falconer, *et al*, found no hyperpotassemia in intestinal obstruction, though they agree that it occurs in animals In fact they noted a tendency for blood potassium to decrease, even more so than blood sodium Greenwood, *et al*, observed that in dogs with high intestinal obstruction there was a fall of plasma potassium of from 17 to 40 per cent in the first few days, followed by a rise prior to death, but in less than half the cases did the value rise higher than the preoperative level Some postmortem plasma specimens had very high potassium values These observers conclude that in dogs changes in plasma potassium do not play an important part in causing death following intestinal obstruction

Loss of Plasma and Tissue Electrolytes After loss of electrolytes through the intestinal wall the concentration of electrolytes in the plasma is a very inadequate measure of the total loss of electrolytes from the organism, for in the absence of an adequate exogenous supply, the loss from the blood is largely replaced by electrolytes derived from the tissue fluids In every 24 hours there may be an actual loss equivalent to all the plasma electrolytes in the body, yet the plasma concentration of electrolytes may be only moderately decreased, e g, fixed base 10 per cent and chloride, 26 per cent, and the total plasma volume

reduced perhaps only 30 to 40 per cent. Under such circumstances the tissues have been drained of their electrolytes to a much greater degree than is indicated by the blood findings Loss of electrolytes may in fact reach the lethal point even when there is practically no change in the serum electrolyte concentration, the hemoglobin and protein concentrations however are increased 25 to 30 per cent in such a case, viscosity is increased 113 to 190 per cent and, more important, the total plasma volume is reduced considerably

Loss of Plasma Volume The shrinkage in plasma volume would appear to be the inevitable serious change which occurs when the electrolyte reserves in the tissue fluids are exhausted and are no longer able to support plasma volume by replacing its lost electrolytes At this stage, since the hemoglobin concentration is above normal, the arterial blood contains an increased amount of oxygen, yet it is not saturated with oxygen as completely as normal blood, probably because the abnormal electrolyte environment renders each unit of hemoglobin less capable of holding oxygen Therefore the net oxygen tension of the blood is reduced, being only about 57 to 65 per cent of normal, this represents a rather severe degree of anoxic anoxemia, which is present despite the excess of hemoglobin in the blood

Fine, *et al* (October, 1940), observed clinically that in small intestinal obstruction, merely decompressing the bowel halted the loss of plasma volume that was taking place, and might even permit the recovery of a substantial fraction of the amount that had been lost Distention of even as little as two feet of the small intestine was found to cause the loss of a significant amount of plasma, whereas distention of the colon failed to do so This difference corresponds well with the marked clinical difference between small and large bowel obstruction These authors are convinced that the decrease in total plasma volume is due to the distention, and not to the obstruction, since it also occurs, they state in severe intestinal distention of functional origin

They noted that the loss of plasma was very great (hematocrit increase of 12 to 25 5 per cent) even in patients who were well hydrated, so dehydration did not seem to be a factor In the normal individual even severe dehydration causes only a moderate increase in hematocrit (7 1 per cent, Coller and Maddock) The plasma loss was generally proportional to the degree of the intestinal distention The magnitude of the plasma loss (30 per cent or more of the total plasma volume) seemed to suggest that it was a basic factor in causing death from obstruction

If this is so then even when decompression of the intestine has been

achieved, it is imperative, as Fine, *et al*, point out, that the plasma deficiency be corrected promptly enough (by means of plasma transfusion) to prevent irreversible changes in vital tissues of the body.

Therapy based on this reasoning was tested in dogs by Fine and Gendel They found that the intravenous injection of plasma in amounts adequate to replace the plasma lost as a result of obstruction and distention of the small intestine markedly prolonged the life of the animals (average 43 hours as compared with an average of 20 8 hours in untreated control animals) The survival time of animals treated with physiological saline infusions alone was somewhat shorter (average 15 8 hours) than that of untreated animals These authors are of the opinion that dehydration and dechloridation are not significant factors in causing the death of animals with intestinal obstruction and distention, though they believe these abnormalities, when present, should be corrected

Azotemia In the course of making determinations of the concentrations of nonprotein nitrogen and urea in a large series of miscellaneous diseases, Tileston and Comfort (1914) discovered that these substances are increased in acute intestinal obstruction, the increase being as marked as in most causes of uremia Of the three cases of intestinal obstruction which they studied, one was a case of mechanical and the other two of paralytic obstruction

Tissue Cell Volume Since the volume of each body fluid is sustained by its total ionic content, dehydration is a result of loss of electrolytes The chief substances maintaining the volume of the blood plasma and the interstitial body fluids are the sodium and chloride ions, because these are the largest fractions of the total ionic content of these fluids They are also the chief inorganic ions in the digestive secretions, for the latter are derived from the plasma Sodium and chloride are not the chief ions in the intracellular fluids, the latter contain larger amounts of K and HPO_4 Even in severe dehydration the intracellular fluids are probably drawn on to only a slight extent because they contain little sodium or chloride, their chief ions being K and HPO_4 This partition of electrolytes serves to defend cell volume

Since intestinal secretion contains approximately the same amounts of fixed base and chloride as blood plasma, its loss does not in itself alter plasma chloride or bicarbonate concentration

It is entirely incorrect to regard plasma chloride concentration as an index of the degree of dehydration or of the extent to which replacement by administration of salt solution is necessary For as mentioned above much more water and salt may have been withdrawn from the body than is indicated by the fall in chloride concentration Progressive de-

hydration, and distortion of the acid base structure of the body fluid can be a sufficient cause for the symptoms and ultimate death in pathological conditions in which there is loss of the digestive secretions from the body

In closed loop obstruction of the intestine the chemical findings in the blood are essentially the same as in simple intestinal obstruction (Haden and Orr, June, 1929)

Suction Drainage in Intestinal Obstruction Penberthy, *et al*, state that if, in intestinal obstruction, the intestine has been decompressed and the patient, during the continuance of intestinal suction drainage, is allowed a full diet and all the fluids by mouth he wishes, there is an excess of intake over drainage in many cases With distention present, however, they rarely observed a positive balance, and until distention is controlled they consider parenteral administration of fluids imperative They feel certain that, in the absence of distention, oral feedings are advantageous in that they decrease the amount of intravenous fluids necessary and afford a better means of controlling the nourishment of the patient.

In the two cases of high jejunal suction drainage which they report, suction removed about half as much of the fluid as was taken by mouth, but the amount of chloride removed by suction was greater than that taken by mouth In general, with suction at high levels in the intestine, it was found to be practically impossible to maintain good balances of nutrition, water, or salt, especially the latter, parenteral fluids were required, but the amount of fluid that could be absorbed from the gastrointestinal tract simultaneously with the suction-drainage seemed to be of decided advantage. In cases of low ileal suction drainage, on the other hand, these observers found it possible to maintain a good fluid, salt, and nutritional balance by the generous ingestion of food, salt, and fluid Nevertheless, they warn that this means of maintaining balance in the presence of intestinal obstruction should not be relied upon entirely

Sedimentation Rate In obstruction of the gastrointestinal tract the erythrocyte sedimentation rate becomes very rapid This change occurs much sooner than the fall in blood chlorides (Haden and Orr, September 1926)

Secretogogues from Obstructed Intestine Dragstedt has reported the toxic' fraction of the fluids from obstructed loops of intestine to be powerful secretogogues for the gastric and other digestive juices although this work has not been confirmed by some other observers Andrus *et al* suggest that possibly the slow absorption of material from the obstructed or strangulated bowel causes death chiefly by stimulating gastric secretion just as histamine does and thereby pro-

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moting the loss of body fluid and electrolytes They found that in dogs with intestinal obstruction much more salt was needed to maintain the blood chloride at the normal level when injections of histamine were given than when not.

Amounts of the Digestive Fluids The average amounts of the various digestive juices secreted per day are as follows (Rowntree)

Secretion	*Cc per day*
Saliva	1500
Gastric Juice	2000 to 3000
Bile	300 to 500
Pancreatic Juice	500 to 800
Intestinal Juice	3000

The digestive secretions altogether therefore amount to about 7 to 9 liters per day This volume is equal to two or three times the total volume of the blood plasma from which the secretions are derived Nearly all of the fluid is reabsorbed in the lower part of the small intestine and in the colon and returned to the blood stream

Intestinal Resection To determine the relation between resection of large portions of the small intestine and mortality or morbidity, Haymond analyzed 257 collected cases He concluded that, discounting the dangers of the operation itself and its possible concomitant complications, a patient can withstand a massive resection of 33 per cent of the length of the small intestine and the digestive tract return to practically normal function, that the removal of 50 per cent of the small intestine constitutes the upper limit of safety, and that above 50 per cent the results are generally poor, though an exceptional case may do well This work has been confirmed by other writers A growing number of cases is being reported in which large percentages of large and small bowel are resected successfully

JEJUNOSTOMY JEJUNAL FEEDING

Allen and Welch believe that obstruction soon after gastroenterostomy is, in most cases, due to edema at the stoma, but they have found that the serum protein concentration is normal in most of the patients, and that the other blood chemical findings are usually within normal limits. Wangensteen is of the opinion that obstruction of the stoma following gastrectomy is due to mechanical obstruction resulting from the turning in of too wide a strip of stomach and intestinal wall at the suture site Allen and Welch have observed that such obstruction is more frequent after posterior gastroenterostomy than after resection of the stomach These authors recommend that, in deciding whether

jejunostomy should be performed in cases of this kind, a careful comparison be made of the volume of fluid taken by mouth with the volume aspirated through the gastroduodenal tube If the amount swallowed exceeds the amount withdrawn, the gastric balance is said to be positive, and vice versa, usually there is a negative balance of 100 to 200 cubic centimeters for the first 48 hours, and then the balance becomes and remains positive

When obstruction develops immediately after operation, which is by far the more common time it occurs, the negative balance on the first postoperative day may be as great as 1 000 cubic centimeters Delayed obstruction most commonly becomes manifest from the 6th to the 8th day, though usually some indications of it are present earlier but are overlooked, or, as Allen and Welch express it, are "clouded by clinical optimism"

With the use of intravenous protein hydrolysate preparations, blood transfusion and plasma it is possible to delay much longer after the development of obstruction following gastric resection and gastroenterostomy than formerly With the use of the Abbott Rawson tube and other types of intestinal tubes jejunal feeding is possible in an increasing number of cases without resort to jejunostomy

Jejunal feeding is often resorted to in surgical conditions, but the very great difficulties associated with its successful accomplishment are not generally appreciated Scott and Ivy have summarized the difficulties as the need for a bland food nonirritating to the gut, which contains enough calories for the daily needs of the body and enough liquid to maintain the normal state of hydration of the tissues, without over distending the bowel causing pain or upsetting the normal digestive processes and producing nausea, vomiting or diarrhea They knew of no instance in which life had been maintained satisfactorily in man or animals solely by jejunal feedings After extensive experimenting they found that the following diet would maintain a dog indefinitely with normal energy and no loss of weight.

Substance	*Amount*	*Calories*
Peptone (dried)	100 gms.	410
Cane Sugar	150 gms	615
Wheat Flour	300 gms.	1091
Milk (whole)	2000 cc	1435
Cream	1000 cc.	1800
Water	3000 cc.	—
	6550 cc	5348 cal

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need of the patient is calculated from the volume of gastric drainage, being taken to be 6 per cent of the latter

Mulholland has used a double-lumened tube in postgastrectomy patients for feeding as recommended by Abbott and has reported that by beginning high protein administrations through the tube into the jejunum, as early as 24 hours postoperatively, it is possible to obviate the necessity of using intravenous fluids after the first two or three days Patients receiving such feedings have normal strength, as tested on an ergograph, within a few days postoperatively and weight loss is much reduced

THE LARGE INTESTINE

MOTILITY OF THE LARGE INTESTINE

Normal Motility of the Large Intestine The entire large intestine exhibits rhythmic variations in tone which have no influence in propelling the contents onward Actual propulsion is accomplished by peristaltic movements, the character of which varies in different portions of the colon In the cecum and ascending colon peristalsis is rather feeble, and weak antiperistaltic waves occur, but only at infrequent intervals This so-called antiperistalsis in the proximal part of the colon is not true peristalsis in that no wave of relaxation precedes the wave of contraction, the process is rather a compression of the contents of the bowel Auer and Krueger (1944) demonstrated that when a loop of the descending colon of a rabbit is delivered through a midline incision, outside the abdomen, and a segment separated from the remainder of the bowel an object moved by peristalsis along the loop can be stopped by digital pressure Its progress will then be reversed by a wave of antiperistalsis, the wave being exactly similar to a peristaltic wave except for a change in direction The anterograde true peristaltic waves in the ascending colon occur at infrequent intervals, most of the contractions being more widespread or general in type

When food is ingested, the entrance of the food into the stomach initiates a gastrocolic reflex which results in mass peristalsis of the entire colon, inducing defecation under certain circumstances Under normal conditions the feces do not pass beyond the rectosigmoid junction excepting at the time of defecation the rectum remaining empty at all other times

Normally a barium meal reaches the cecum in about 4½ hours after ingestion, the hepatic flexure six hours, splenic flexure nine, descending colon 11, iliac colon 12 and pelvic colon 18 hours after ingestion

The chief function of the large intestine is the absorption of liquid

Of this mixture the dog requires 100 cubic centimeters per kilogram body weight, the human infant requires about this same amount, the adult somewhat less Each 100 cubic centimeters is approximately equivalent to 80 calories, containing

Protein	3 5 gms	13 cal
Carbohydrate	8 1 gms	31 cal
Fat	4 3 gms	36 cal

Additional water may be given according to thirst, and sodium chloride may be added in an amount sufficient to maintain chloride balance Moreover, to the daily feeding are added the following vitamin substances

Cod liver oil emulsified in bile, 10 cubic centimeters
Viosterol, 2 to 5 drops
Egg yolk, 1
Vitamin B concentrate (Harris), 1 gm
Yeast "foam," 0 5 cubic centimeters
Tomato juice, neutralized, 20 cubic centimeters

It was found that glucose was more irritating than cane sugar, that raw fruit juices irritate, and that fresh moist yeast caused diarrhea The pH of the mixture is approximately 6 0

Double-lumened Tube Predigestion of the food given is desirable in jejunal feeding, but as Abbott points out, the more advanced the predigestion is, the more irritating are the resulting products unless their concentration is correspondingly reduced, and this of course decreases the calories supplied Abbott found that the normal fasting jejunal contents are usually hypotonic and that their maximum glucose concentration after ingestion of glucose is 6 per cent In view of these and other facts he advises for the post-gastroenterostomy or gastrectomy patient the following jejunal feeding administered through a double-lumened tube which he has devised, the shorter portion of the tube extending only into the stomach and being used for continuous gastric suction, the longer portion extending through the stoma into the jejunum.

Acidified skim milk, incubated with commercial pepsin
Dextrose, 6 gm per 100 cubic centimeters
Sodium bicarbonate, to neutralization
Viosterol in fish liver oil, 1 cubic centimeter }
Thiamin chloride, 20 milligrams } per day
Nicotinic acid, 50 milligrams }
Ascorbic acid, 100 milligrams }

This mixture has a high protein, a relatively high carbohydrate, and a low fat content It yields about 1500 calories per 2½ liters The salt

positive activity of the sacral parasympathetic (motor) supply and inactivity or diminished activity of the sympathetic (inhibitory) supply. The stimulus which normally initiates the afferent impulses which bring about the appropriate activity of the afferent nerves is distention of the rectum, which stimulates the nerve endings of "muscle sense" in its muscular coat, as shown by Hurst, the mucosa of the rectum has no sensory nerve endings except in the anal canal

The process is complicated, however, by the necessity for the co-operation of the skeletal muscles and the sequence of events is probably as follows Mechanical pressure upon the rectal wall causes impulses to ascend to the sacral segments of the spinal cord where they stimulate the center of the sacral nerve supply of the bowel, so that recurring waves of contraction of the colon result. The original afferent impulses initiated by the pressure continue up the spinal cord to the brain and bring about a subjective sensation interpreted as the urge to defecate The waves of contraction of the colon already reflexly induced initiate more afferent impulses (of colon "muscle sense") which in turn reach the brain and intensify the sensation In response to this reinforced urge the individual may voluntarily cause the appropriate skeletal muscles to contract and the external sphincter ani (which is under the control of the will) to relax At this stage it is necessary that a strong co-ordinated contraction of the colon take place and that the internal sphincter relax.

The individual cannot induce these latter smooth muscle effects directly by any act of the will and presumably they are brought about indirectly as follows When the abdominal and other skeletal muscles are made to contract and the external sphincter to relax voluntarily as just described, sensory (proprioceptor) endings in these striated muscles are stimulated by the change in tension and give rise to a group or "pattern" of afferent impulses which enter the central nervous system and excite in an appropriate manner the autonomic nerves which control the bowel and internal sphincter In this way proper co-ordinated contraction of the colon and relaxation of the internal anal sphincter are brought about

The external anal sphincter, though it is composed of striated muscle behaves like smooth muscle in many respects It does not degenerate after sectioning of its nerve supply The internal sphincter (smooth muscle) is usually competent when the external has been divided In injuries to the sphincter muscles and in sphincter saving operations upon the rectum, it has been found that although the external sphincter is competent lack of the internal sphincter makes complete

from the material received from the small intestine This absorption is performed mainly by the cecum and ascending colon, partly by the pelvic colon Very little absorption occurs in the transverse and descending colon

There are, therefore, three functional divisions of the large intestine (1) From the ileocecal junction to the middle of the transverse colon This is the only segment in which antiperistalsis occurs normally These reverse waves may perhaps have some relation to the development of appendicitis There is normally considerable delay in this region in the onward movement of the bowel contents A fistula at this level is attended with more or less continuous discharge of quite liquid feces (2) From the middle of the transverse colon to the lower sigmoid In this segment there occur slow contraction waves and also so-called "large colonic movements " The latter occur especially just after meals A fistula in this region gives rise to quite regular stools of soft or solid feces one to three times a day. (3) The lower sigmoid and rectum

The sacral autonomic (parasympathetic) nerves motivate the entire colon perhaps with the exception of the ascending and the right half of the transverse colon, and are inhibitory to the internal sphincter ani The sympathetic nerve supply is inhibitory to the whole large intestine as it is to the small intestine, but motor to the internal sphincter ani, that is, it induces closure of the sphincter

Wells, Mercer, Gray, and Ivy (1942) demonstrated by electrical stimulation of the pelvic nerves in the dogs that those nerves influence the upper levels of the colon by way of nerve pathways located in the wall of the intestine They were unable to demonstrate a dual contractile and tonus mechanism in response to pelvic nerve stimulation in the colon as has been claimed to exist in the urinary bladder Electrical stimulation of the vagus nerve was ineffective in producing a response in the colon in the dog Electrical stimulation of the hypogastric nerves produced a circular contraction which was confined to the distal colon Electrical stimulation of the pelvic nerves produced longitudinal and circular contractions in the descending and distal colon Due to the decrease in hyperemia of the rectum and lower colon in individuals with ulcerative colitis following vagotomy, under circumstances of emotional strain, Dennis has suggested that the vagus nerve may have some influence on the lower sections of the colon and even of the rectum

The Mechanism of Defecation Defecation consists of co-ordinated movements which bring about emptying of the colon from about the middle of its transverse portion to the anus. Normally it involves simultaneous cooperation of both nerve supplies of the large bowel, that is,

Intestinal Pain By means of a balloon which is passed the entire length of the intestinal tract in man and inflated at different levels, Jones and Pierce studied the reference of intestinal pain They confirmed the general clinical observation that pain originating in almost any level of the small bowel is referred to the midline just above or just below the umbilicus, and occasionally to the back Pain from the cecum was referred to McBurney's point with a spread to the epigastrium, hepatic flexure pain was referred to the right upper quadrant In the ascending, transverse and descending portions of the colon, pain was referred for the most part to the lower abdomen near the midline or somewhat to the left Pain from the rectosigmoid part of the colon was felt either in the suprapubic or coccygeal region In general, reference of pain from the fixed parts of the large bowel was fairly well localized near the point of stimulation, whereas pain from the more mobile parts tended to spread toward the midline well away from the point of stimulation

SECRETION AND ABSORPTION IN THE LARGE INTESTINE

The large intestine secretes only mucus and hence has no digestive function Normally it probably absorbs only salts, water and gases, but it is believed to be capable of absorbing a limited amount of dextrose and a number of other water soluble substances From experiments on 50 normal adults, Scott and Zweighaft concluded that there is no evidence of absorption of dextrose by the rectum when given in 10 per cent solution Cutting likewise found that the hypertonic solutions often used are poorly absorbed, having an osmotic action and causing irritation He points out that determinations of the blood sugar level cannot be used as an index of absorption since the blood sugar content is a variable determined by the interplay of many factors, and is in a continuous state of flux Determining the local portal blood sugar level is likewise useless Changes in respiratory quotient, used by some experimenters to measure rectal absorption of dextrose, really measure utilization of dextrose, not absorption Cutting found only a fair amount of absorption from a 5 per cent approximately isotonic dextrose solution On the other hand Collens and Boas found that hypoglycemia in a diabetic patient caused by an overdose of insulin was immediately relieved by the administration of 25 grams of dextrose by rectum

Possibly the absorptive ability of the bowel for dextrose is abnormally increased in the presence of marked hypoglycemia That it is negligible under ordinary conditions is generally agreed Perusse tried many different solutions in the dog and in man and concluded that 1 per cent

anal continence impossible When the rectum becomes filled an automatic mechanism apparently comes into play which increases the tone of the internal sphincter and aids greatly in control Since the external sphincter is largely a voluntary muscle and is not constantly in a state of tone, it is not well suited to provide complete involuntary control When the extrinsic nerves of both sphincters have been severed, the local ganglion cells gradually come to act as an anal center, developing tone and establishing continence so that evacuation occurs only intermittently

White, *et al* (Dec, 1940), studied various neurogenic disturbances of the colon by means of the "colonmetrogram," which is a recording of pressure changes within the bowel They found that the normal person becomes aware of a sensation of filling in the colon at a pressure between 20 and 30 cm of water, has real urge to defecate at 40 or 50 cm and at higher pressures experiences distinct low abdominal pain Lesions of the brain, spinal cord, and sacral nerves produced characteristic changes in the colonmetrogram These changes depend, to a large extent, on the degree of sensory loss, the severest grades of paralysis being found in patients with degenerative diseases of the sensory fibers in the sacral cord These authors state that one can evaluate neurologic disturbances of defecation by this method They found no changes in bowel function after bilateral lumbar ganglionectomy, or after bilateral splanchnicectomy with removal of the upper lumbar ganglia

Megacolon In congenital megacolon, enormous dilatation of the large bowel occurs down to the region of the rectosigmoid Although it was formerly considered that this was due to a pathological process limited to the dilated portion of the colon, Swenson (1950) pointed out several features of the disease which appeared to be inconsistent with this point of view 1 Colostomy relieves all of the symptoms within three to six months, 2 Barium enema studies reveal an irregular funnel-shaped outline of the rectosigmoid, 3 The dilated portion of the colon has normal integrated peristalsis, 4 Resection of the functionally deficient segment relieves the symptoms, 5 Histological study of the specimens removed has demonstrated an absence of Auerbach's plexus in the rectosigmoid Since it is known that peristalsis cannot take place in a bowel in which Auerbach's plexus has been destroyed, this narrowed segment produces mechanical obstruction which results in the huge dilatation of the proximal portions of the colon Resection of the abnormal rectosigmoid by a pull through technic has given gratifying results

TABLE XI

NON RESIDUE DIET BEFORE COLON OPERATION

(From Bargen and Victor)

Breakfast	Dinner	Supper
Fruit juice any kind 1 glass Heavy cream, 4 table spoonfuls Egg 1 Butter 1 square Arrowroot cookies 2 Coffee* 9 A.M. Candy 5 ounces either pure sugar candy or milk chocolate without nuts	Broth with 1 square of butter Gelatin plain 2 heaping tablespoonfuls Heavy cream 4 table spoonfuls Fruit juice any kind, 1 glass Arrowroot cookies 2 Tea or coffee* 3 P M Fruit juice any kind 1 glass	Broth with 1 square of butter Steamed rice 2 heaping tablespoonfuls* Heavy cream 4 table-spoonfuls Fruit juice any kind 1 glass Arrowroot cookies 2 Tea or coffee*

* Sugar for tea, coffee and rice as desired.

A postoperative diet for patients who have recently undergone colostomy should have (1) low water content, (2) low residue con tent and (3) concentrated food Later the diet can usually approach the ordinary mixed diet Bargen and Victor suggest the postcolostomy diet given in Table XII

TABLE XII

DIET FOR PATIENT WHO HAS UNDERGONE COLOSTOMY

(From Bargen and Victor)

Breakfast	Dinner	Supper
Orange juice ½ glass Bacon or egg 1 serving Toast, as desired Butter as desired Coffee, if desired Brewers yeast	Meat 1 serving Potato 1 serving Shredded lettuce 1 serving Bland dessert no fruit Bread toast or crackers as desired Butter as desired Jelly if desired Milk (boiled) 1 glass Tea, if desired Brewers yeast	Cheese 1 serving Meat, 1 serving or 2 eggs Potato or substitute Fruit ripe banana or other bland fruit Bread crackers or zwieback, as desired Butter as desired Jelly if desired Milk (boiled) 1 glass Brewers yeast

W S McCune, M D

dextrose solution is absorbed the best Helwig, *et al*, report a case of fatal water intoxication caused by the absorption of 9 liters of tap water by proctoclysis within a period of 30 hours following cholecystectomy. The colon cannot absorb proteins or fats and therefore the possibilities of feeding per rectum are very limited Pogrund and Steggerda (1946) have demonstrated that the rate of absorption of gas from the colon in man depends upon the partial pressure gradient between the lumen and the venous blood of the gas concerned The average blood tension of oxygen was found to be 3 52 volumes per cent and that of carbon dioxide 6 86 volumes per cent The blood tension of nitrogen is approximately 80 per cent which accounts for the retarded absorption of this gas from the colon The colon normally excretes 95 per cent of the calcium eliminated from the body and also is the chief excretory organ for certain foreign substances, especially the heavy metals such as iron, bismuth and mercury

Meyer, Gellhorn, *et al* (1949) have described a mucolytic enzyme which they designate lipozyme This enzyme removes the surface mucus of the intestinal mucosa It is present in greatly increased amounts in stools of individuals with chronic ulcerative colitis and it has been found that the lipozyme titre of the stools falls with clinical improvement When fed to dogs it will produce gastric, small intestinal and colonic ulcerations Because of these findings the authors believe lipozyme to be a possible etiologic agent which locally initiates the lesions of chronic ulcerative colitis.

Effects of Colectomy Ileostomy with total colectomy or colonic exclusion does not cause any permanent deficiencies in metabolism or disturb the chemical composition of the blood except for a slight reduction of serum calcium with return to normal within a month, as shown by Whittaker[1] and Bargen These observers found that the average weight of the stools from the ileum was 433 grams and the water content 91 2 per cent while the patients were on a general diet The discharge was watery at first, gradually becoming thicker during the first three months A period of three months was necessary for the patients to regain their normal weight and strength

DIETARY IN SURGERY OF THE LARGE INTESTINE

The principles upon which a preoperative diet in cases of operation on the colon is based, as expressed by Bargen and Victor, are (1) high food value, (2) relative freedom from residue, and (3) favorable effect on the intestinal flora A diet of approximately 2300 calories which they recommend fulfilling these requirements is given in Table XI

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Chapter X

THE PANCREAS

UNLIKE the other organs that make up the endocrine system, the pancreas produces both internal and external secretions The internal secretions have an effect on the regulation of carbohydrate metabolism (insulin) and an influence on fat utilization by the liver (lipocaic) The external secretions (pancreatic juices) are concerned with the digestion of proteins (trypsin), carbohydrates (amylase) and fats (lipase)

Embryologically, the pancreas arises from two sources A ventral anlage arises in conjunction with the bile ducts and a dorsal outgrowth comes directly off the distal portion of the foregut Fusion of these two outpouchings with later rotation gives rise to the complete organ and explains its transverse position The primitive ventral portion ultimately becomes the head of the pancreas and communicates with the bile duct by means of the duct of Wirsung The dorsal portion makes up the remainder of the organ (neck, body and tail) which drains by means of the duct of Santorini Variations in the duct of Santorini occur which may have clinical implications in that it may empty into the duct of Wirsung, into the common duct, or directly into the duodenum at a site away from the papilla of Vater. In this latter instance, the sphincter of Oddi would not appear to have any affect on external secretory drainage from the major portion of the pancreas

Internal Secretions The internal secretions, insulin and lipocaic, have their own individual characteristics and effects upon the carbohydrates and fats respectively

Insulin Insulin is a protein with a molecular weight of 35,000 It may be crystallized in the presence of zinc or other heavy metals, but the physiological effectiveness of crystalline insulin and the amorphous form is essentially similar

Action of Insulin The administration of insulin (1) initiates or accelerates oxidation of carbohydrates by muscles and other tissues, (2) restores liver glycogen (3) diminishes nitrogen excretion and (4) eliminates ketosis in the diabetic animal or man

The effect of the internal secretions of the pituitary, adrenals, and thyroid on insulin has been the subject of much discussion and investigation Price Cori and Colowick have shown that both in vitro and in

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reaction of the body fluids is shifted toward the acid side For this reason, asphyxia impairs the action of insulin The products of infection and also all general anesthetics interfere in some unknown way with the action of insulin

Five internal secretions are more or less antagonistic to insulin, (1) antuitary diabetogenic substance, (2) postuitary extract (it is not known which fraction), (3) thyroxin, (4) adrenalin, and (5) adrenal cortex hormone

The pancreas is not essential to sugar oxidation or glycogen formation (just as the autonomic nerves are not essential to smooth muscle contraction and relaxation), for the "Houssay dog" (pancreas and pituitary removed) is able to metabolize sugar The dextrose tolerance test is normal and the liver and muscle glycogen contents are normal in such animals

Kotte and Vonderahe report a case of the Houssay phenomenon in man, a patient with diabetes mellitus had severe terminal hypoglycemia associated with an infarct of the pituitary body with destruction of the anterior lobe.

Diabetes Diabetes is a condition characterized by the organism's inability to utilize carbohydrate in a normal manner, and is manifested by hyperglycemia and glycosuria. Its pathogenesis is varied and may derive from (1) insulin deficiency, (2) pituitary hyperfunction, or (3) adrenocortical hyperfunction Its treatment rests on the balance between dietary intake, exercise and insulin

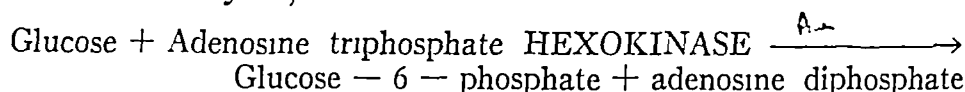
Diabetes may be produced experimentally by (1) pancreatectomy, (2) continued anterior pituitary extract administration, (3) administration of ACTH, compounds E and F, and (4) administration of alloxan which causes a specific degeneration of Langerhans' cells

Diabetes may conceivably be caused by three different factors 1 Hypoinsulinism, e g , destruction or paralysis of the islands of the pancreas leading to increased glucose formation 2 Hyperantuitarism, e g , excess of antuitary diabetogenic substance, which stimulates the liver to put out an excess of glucose 3 Nonendocrine causes, e g , primary liver disturbances

Probably all of these factors overlap in clinical cases of diabetes and in addition there may be an insufficient utilization of glucose by the tissues, the cause of the latter being unknown The favorable effect of insulin is obtainable in all cases and gives no indication of the factor or factors responsible for the disturbance of glucose production or utilization

Spontaneous Hypoglycemia Spontaneous hyp[illegible]

living animals, extracts of the anterior lobe of the pituitary inhibit the action of the enzyme, hexokinase



Glucose + Adenosine triphosphate HEXOKINASE ⟶ Glucose − 6 − phosphate + adenosine diphosphate

Insulin diminishes or abolishes this inhibitory action of the anterior pituitary This gives a partial explanation of the "Houssay dog" (pancreas and pituitary removed), but does not explain the peculiar sensitivity of the Houssay dog to the hypoglycemic effect of insulin

The effect of total pancreatectomy in the dog and cat is not due to absence of pancreas alone, but also to activity of the anterior pituitary Animals in which the hypophyses have been removed are excessively sensitive to insulin This can be counteracted by anterior pituitary extract Anterior pituitary hormones directly inhibit the combustion of carbohydrates by the tissues in the presence or the absence of the pancreas Repeated injections of anterior pituitary extract can produce permanent diabetes and degeneration of the islands of Langerhans in the normal dog The over-all effects of the active principles of the anterior pituitary on carbohydrate metabolism are 1 Retarded utilization of muscle glycogen, 2 Diminished ability to oxidize carbohydrates, 3 Increased formation of liver glycogen from protein

Epinephrine is not directly antagonistic to insulin Epinephrine mobilizes liver glycogen and muscle glycogen to produce glucose and lactic acid, respectively The latter enters the blood and finds its way to the liver where it is formed into glycogen, and this becomes the source of more glucose

In experiments on normal humans Conn has shown that clinical diabetes mellitus may be produced by administration of adrenocorticotropic hormone (ACTH) This diabetes was found to be resistant to insulin administration

Investigations by Long and by Kendall indicate that Compounds E and F may be potentially diabetogenic since they increase glucogenesis from protein

The thyroid does not interfere with utilization of carbohydrates According to Peters and Van Slyke it only affects carbohydrate metabolism secondarily by accelerating total body energy expenditure

The action of insulin is to lower the percentage of sugar in the blood and favor its storage and utilization, in the form of glycogen, in the liver, muscles and skin The maximum effect of an injection occurs in an hour This is in contrast to taking of food, which has its peak effect of raising the blood sugar in half an hour However, both these time factors are subject to variation Insulin is less effective when the

TABLE XIII

ETIOLOGIC CLASSIFICATION OF SPONTANEOUS HYPOGLYCEMIA

I Organic—recognizable anatomic lesion.
  (a) Hyperinsulinism
    1 Pancreatic island cell carcinoma
    2 Pancreatic island cell adenoma.
    3 Generalized hypertrophy and hyperplasia of the islands of Langerhans.
  (b) Hepatic disease.
    1 Ascending infectious cholangiolitis.
    2 Toxic hepatitis.
    3 Diffuse carcinomatosis.
    4 Fatty degeneration. "Fatty metamorphosis
    5 Glycogenosis (von Gierke s disease)
  (c) Pituitary hypofunction (anterior lobe)
    1 Destructive lesions (chromophobe tumors cysts)
    2 Atrophy and degeneration (Simmonds disease)
    3 Thyroid hypofunction (? secondary to pituitary hypofunction)
  (d) Adrenal cortex hypofunction.
    1 Idiopathic cortical atrophy
    2 Destructive infectious granulomas
    3 Destructive neoplasms.
  (e) Central nervous system lesions (lesions of brain and brain stem said to interfere with nervous control of blood sugar)
II. Functional—no recognized anatomic lesion.
  (a) Hyperinsulinism (? autonomic nervous system imbalance)
  (b) Renal glycosuria (severe degree of low renal threshold for dextrose)
  (c) Severe continuous muscular work.
  (d) Pregnancy and lactation.

Effect of Diet Dietary measures are notoriously unsuccessful in organic hyperinsulinism, but are efficacious in controlling functional hyperinsulinism Diets high in carbohydrate content result frequently in an increased number of attacks of greater severity This is due to the fact that the postprandial rise of blood sugar produced by the ingestion of large amounts of easily assimilated carbohydrate stimulates insulin secretion so that there is an abrupt fall of blood sugar to hypoglycemic levels Conn found that a diet high in protein and low in carbohydrate is beneficial in hyperinsulinism, and could be given on a three meal schedule Though protein during its metabolism yields approximately 50 per cent of its weight as dextrose, the ingestion of large amounts of protein is followed by little or no rise in blood sugar when an equivalent amount of dextrose is ingested, as such or as carbohydrate food, a significant hyperglycemia is produced The therapeutic effectiveness of the high protein diet is ascribed to (1) slow even rate at which dextrose

to hyperinsulinism in every case It may be caused by deficiency of antuitary diabetogenic hormone or adrenal cortex hormone, by liver injury and probably by other factors Primary hyperinsulinism is established as the cause when removal of an islet cell tumor corrects the hypoglycemia General hyperplasia of the islet tissue of the pancreas without localized adenoma might conceivably occur but this has not been proved Even when partial pancreatectomy relieves the condition, this fact does not establish overactivity of the islet cells as the cause The actual cause may still be deficiency of antuitary diabetogenic substance, for in that case removal of part of the pancreas would give relief by restoring the balance between the two hormones When the antuitary is completely extirpated, the resultant hypoglycemia can be alleviated by complete removal of the normal pancreas, the two endocrine factors influencing production and utilization of sugar in opposite directions are thereby balanced at a new lower level The typical signs of profound hypoglycemia are dependent on loss of function integrity of the nerve cells in the higher centers of the brain This is proved by the fact that in a decerebrate animal or in one under a general anesthetic, hypoglycemia produces no physical signs.

The importance of etiology in determining the treatment of the spontaneous hypoglycemias is emphasized by Conn

Conn points out that 80 to 90 per cent of all cases of spontaneous hypoglycemia fall into three groups, namely, in order of frequency, functional hyperinsulinism, organic hyperinsulinism and hepatic disease He gives the following indications for surgical exploration and treatment A *Pancreas* 1 Absence of extrahepatic causes of hypoglycemia 2 Abnormally low level of blood sugar during symptoms, and rapid relief of symptoms by the administration of dextrose 3 Repeated fasting blood sugar values below 50 milligrams per hundred cubic centimeters when the patient has been eating an adequate diet 4 Depression of the fasting blood sugar below 40 milligrams per hundred cubic centimeters by carbohydrate restriction B *Cholecystectomy* (This operation would be performed in appropriate cases to remove the source of ascending hepatitis and thus allow a return to normal liver function) 1 Postabsorptive hypoglycemia, markedly intensified by restriction of dietary carbohydrate 2 Postprandial hyperglycemia with intermittent glycosuria 3 Hyperglycemia plateau type of dextrose tolerance curve with abnormally low fasting level 4 Evidence of impaired liver function by other tests 5 Evidence of diseased gallbladder by cholecystography 6 Presumptive elimination of other causes of chronic degenerative and destructive lesions of the liver

anesthetics, where applicable, are favorable to the diabetic requiring surgery Wilcox and Tovell report satisfactory results using sodium pentothal anesthesia in cases complicated by diabetes

LIPOCAIC

Lipocaic is a postulated internal secretion of the pancreas which has the property of preventing or curing the fatty degeneration of the liver which regularly develops in the dog in which pancreatectomy has been performed (Dragstedt, *et al*, 1936) The fatty degeneration of the liver following complete pancreatectomy is presumed to occur because of the lack of this hormone Lipocaic is found in extracts of the pancreas, and is distinct from choline, although possessing some of its properties (Ivy and Gray) Dragstedt believes it may be secreted by the alpha cells of the islets of Langerhans

Cole and Howe report a case of severe fatty infiltration of the liver associated with fibrosis of the pancreas and cite experimental and clinical evidence that the liver lesion was secondary to pancreatic insufficiency They found lipocaic very helpful in the treatment They suggest that this "pancreaticohepatic syndrome" is the same disease as pancreatic steatorrhea of childhood, and that the etiology may be variable, perhaps in the form of pancreatic stones, gallbladder disease or possible deficiency of some other gland in adults,

There is an antifatty liver factor contained in the external secretion of the pancreas This was demonstrated by Montgomery, *et al*, in dogs maintained with insulin and fed varied diets, in which pancreatectomy had been performed

While small amounts of pancreatic glandular tissue are sufficient to maintain a normal lipid content in the liver of the dog which has had the pancreas removed lipocaic is a poor source of the antifatty liver factor of the pancreas

The experiments of Dragstedt and his associates were repeated by Canepa, *et al*, with a slightly modified fat free pancreatic extract. They found that the formation of a fatty liver in the dog, after pancreatectomy, was prevented by administration of this extract However, they found a persistence of hypoprothrombinemia when all other blood components returned to normal levels and suggested that some liver cell injury persisted and could not be completely corrected by the lipotropic principle of the pancreas

External Secretions The external secretion is regulated by the hormonal stimulation of the gland and by nervous stimulation through the vagus and splanchnic nerves The secretion resulting from hormonal

is formed from protein, so that there is no elevation of the blood sugar level and, therefore, no secondary fall, and (2) the prolonged period required for the absorption of protein and its conversion to dextrose, so that there is a prolonged and steady supply of dextrose to the blood stream The occasional addition of a protein meal at bedtime has been found desirable in these cases The average diet as recommended by Conn contains from 120 to 140 grams of protein, from 50 to 75 grams of carbohydrate and sufficient fat for maintenance of total calories That is, about two grams of protein per kilogram of body weight are given

The rapidity with which the blood sugar drops is of importance in determining the severity of the hypoglycemic symptoms produced

Cases of hypoglycemia of indeterminate origin have been reported in which severe hypoglycemic episodes continued to occur even after practically all pancreatic tissue had been removed by one or more operations Kepler mentions instances of this kind in which necropsy failed to reveal an adequate basis for the occurrence of the hypoglycemia He calls attention to the fact that it is customary to include hypopituitarism among the causes of hypoglycemia, whereas, actually hypoglycemia symptoms are rarely encountered in cases of hypopituitarism

David gives the following indications for pancreatectomy for hypoglycemia The first requirement is the presence of the "Whipple triad," consisting of (1) nervous or gastrointestinal attacks occurring during fasting, associated with (2) hypoglycemia, below 50 milligrams per cent, and (3) relieved immediately by the ingestion of glucose One should then exclude extrapancreatic causes for the syndrome, and having done so, explore for an islet tumor of the pancreas If this is not found, there is a clear indication for subtotal resection of the tail and body of the pancreas up to the superior mesenteric vessels David reports from the literature 17 cases treated in this manner with favorable results

Ketone Substances In normal blood small amounts of ketone substances are present Therefore, it is preferable to consider these substances as normal intermediate products in the oxidation of fatty acids, when the rate of breakdown of the latter is excessive, as in pancreatic diabetes, the ketone bodies accumulate in the blood Betaoxybutyric acid is relatively nontoxic, acetoacetic acid is more toxic

Anesthesia in Diabetics · Although insulin permits the use of almost any type of anesthesia, certain agents carry a greater threat to the diabetic patient undergoing surgery Joslin and co-workers feel that anesthetics or combinations of anesthetics which tend to produce anoxia are of particular danger to the diabetic patient Spinal and local

Though the clinical diagnosis can often be made by relatively simple tests, Beazell, *et al*, state that an absolutely unequivocal diagnosis of exclusion of pancreatic juice, it is necessary to demonstrate 1 Absence of pancreatic enzymes from the duodenal drainage fluid 2 An excess of both fat and nitrogen in the feces 3 A reduction in the waste of both fat and nitrogen following substitution therapy with pancreatic enzymes These authors administered 8 grams of pancreatin three times a day in the form of enteric coated tablets, at this rate, the total daily dosage is equivalent to 240 cubic centimeters of pancreatic juice, which represents only about 15 per cent of the amount estimated to be secreted normally in 24 hours This enzyme therapy decreased the amount of fat excreted in the feces by an average of 63 3 per cent and decreased the amount of nitrogen excreted in the feces by an average of 62 per cent Clinical benefit became manifest in a few days, characterized by a decrease in the frequency and bulk of the stools and a gain in weight and strength

In a case subjected to total pancreatectomy, Dixon, *et al*, found that 15 grams daily of enteric coated concentrated pancreatin reduced the loss of fat and protein by approximately 50 per cent The amounts of fat and nitrogen lost, however, were in excess of normal values

Secretion of pancreatic juice begins one or two minutes after the beginning of a meal, the rate of flow increasing markedly when food starts to enter the duodenum Secretion continues for about two or three hours In a case of pancreatic fistula in man, following successful resection for cancer of the ampulla of Vater, Snyder and Lium intubated Wirsung's duct and observed the volume of secretion The flow was continuous, the rate varying from 12 to 26 drops per minute The average 24 hour secretion was 1,167 cubic centimeters, the maximum for a single day being 1,384 cubic centimeters The output during the daytime was double that of the night

Control of Pancreatic Secretion The activity of the pancreas is regulated by both nervous and chemical reactions, the former being probably the more important The vagus is the nerve of supply Experimentally, on stimulation and after a rather long latent period, the vagus induces secretion of a viscid fluid, rich in enzymes An inhibitory nerve supply has not been demonstrated, sympathetic fibers enter the pancreas along the blood vessels, but are believed to be vasomotor in function

It is believed that the vagus exerts its effect on the pancreas by producing vasodilatation, but Crider and Thomas suggest that vagal influence on external secretion of the pancreas is through augmentation or inhibition of local reflexes If the vasoconstrictor effect is

stimulation is thin and watery and made up principally of inorganic material, and the secretion arising from nervous stimulation through the vagus or splanchnic nerves is of a thick, tenacious character and contains the highest concentration of enzymatic substances necessary to the digestive process Food is the common stimulus for either mechanism

Extracts of the pancreas itself are very acid in reaction, therefore there is a need for secretions to neutralize this alkaline reaction These secretions are (1) *trypsin,* which when first secreted is inactive, but is transformed into an active protein-splitting enzyme by interaction with enterokinase of the intestinal juice in the presence of calcium By this action, the split protein molecule is changed to amino acids and can be absorbed and used for metabolism, (2) *amylase,* which causes an hydrolysis of starch into maltose and achroodextrin, which are in turn acted upon by the maltase of the intestinal secretion, converted into dextrose, and absorbed for the carbohydrate metabolism, and (3) *lipase,* the fat-splitting enzyme which is responsible for the digestion of the greater part of all ingested fat

In the normal individual the total fecal fat should not exceed 20 per cent of the dried stool The fat loss in the stools should be no more than five to seven per cent of the fat ingested

When large amounts of undigested food are found in the feces, the diseased pancreas is so far progressed that it has completely or almost completely cut off the supply of pancreatic juice to the intestine In such cases, 30 to 70 per cent of the nitrogenous material and 40 to 60 per cent of the fat taken in the diet appear in the feces, the relative amounts varying with the amount of bile secreted, the motility, secretion and absorption of the intestine, as well as other factors

If, for any reason, the external secretion of the pancreas is deficient in amount or is lost from the body, the diet should contain little fat but a considerable amount of carbohydrate, since the latter can still be digested satisfactorily by the intestinal enzymes, predigested protein should be given because of the lack of trypsin

Exclusion of pancreatic juice from the intestine results in an increase of fat, nitrogen, starch and total carbohydrate in the feces It is only in pancreatic achylia that failure of fat utilization is paralleled by a concomitant failure in protein utilization In some cases, there are large quantities of meat fibers in the feces when chemical examination reveals that the total nitrogen is only slightly greater than normal The presence of meat fibers in the stool, therefore, may be misleading as an index to total nitrogen Enzyme therapy effects a significant increase in the utilization of fat and protein in pancreatic achylia

and pancreatic secretions (except amylase) all decrease in quantity and in enzyme content, in spite of which these secretory mechanisms are capable of response under stimulation

In addition to its influence upon the pancreas, secretin to some extent stimulates the intestinal glands to secrete and also accelerates the secretion of bile by the liver, but it is not known whether these two functions are of any appreciable importance under physiological conditions The ingestion of fats is stated by Pavlov to stimulate pancreatic secretion Snyder and Lium, however, found that carbohydrate (glucose) was the only type of food that caused increased secretion They also observed that pilocarpine and physostigmine had a stimulating action Alkaline solutions by mouth inhibit pancreatic secretion, reducing particularly the water and alkali content of whatever secretion is produced According to Lahey and Lium, soda given by mouth in large amounts lessens pancreatic secretion, and the diet which causes the least secretion is one high in fat and low in carbohydrate Craft found experimentally that ephedrine, like adrenalin, decreases the output of pancreatic juice on an average of 31 2 per cent, he recommends its use for the management of patients having a pancreatic fistula

Loss of Pancreatic Secretion Elman and McCaughan, in 1927, showed experimentally that loss of the entire external secretion of the pancreas is fatal in five to eight days in the dog Large amounts of pancreatic juice are secreted up to the time of death, in fact, the largest amounts are secreted in the later days of the experiment in spite of the depletion of body fluids due to lack of intake and to the persistent vomiting which occurs The cause of the vomiting is not known it is probably due to absence of regurgitation of the alkaline pancreatic juice into the stomach which normally occurs As a result of the loss of the pancreatic juice, marked dehydration occurs and the red cells of the blood increase Blood chloride decreases and alkalosis develops, pH rising these changes must be ascribed to the coincident loss of gastric juice rather than to loss of the alkaline pancreatic juice The blood sugar remains unchanged

A case of pancreatic fistula in which the patient reingested the discharged pancreatic fluid is reported by Cathala and Seneque Before reingestion was begun the patient steadily lost weight and strength, about 500 cubic centimeters of fluid were lost each day For nearly two weeks the patient drank pancreatic fluid removed from the fistula, with striking disappearance of vomiting and digestive disturbances, increase in weight and general increase in physical vigor Pancreaticogastrostomy was then performed

Total loss of external pancreatic secretion in the dog, from which

reduced sympathetic stimulation also has a stimulating effect on the increased flow of pancreatic juice

Secretin: The chemical regulation of pancreatic secretion by secretin is a classical instance of hormone control and was the first hormonal mechanism to be demonstrated Secretin is a substance, believed to be a polypeptide which is formed by the action of hydrochloric acid upon some substance formed in the intestinal mucosa All parts of the small intestine can produce secretin but more is produced in the upper segments It is thought that perhaps the presence of bile in the duodenum is necessary for secretin mechanism acidified bile being required for the proper absorption of the secretin bile mucin is believed by some to slow the absorption and so prolong the effect

After absorption into the circulation secretin is carried throughout the body and upon reaching the pancreas stimulates it to secrete The resulting secretion trypsin is thin and watery, is very alkaline in reaction and contains much inorganic material whereas it is very poor in enzymes. In all these respects it differs from the secretion produced in response to vagus stimulation. Thus vagal secretion contains active trypsin instead of inactive trypsinogen. The secretin mechanism is not an absolute necessity for satisfactory pancreatic secretion, since the latter occurs in cases of achylia gastrica when there is no hydrochloric acid available for secretin formation

Diamond and Siegel have found that secretin is a potent stimulus to the pancreas a dose of 0 75 milligrams per kilogram of body weight causing a marked flow of pancreatic juice In pathological states of the pancreas the enzyme content of the pancreatic juice is decreased earlier and more markedly than the volume secreted or the bicarbonate content One enzyme may be more effected than the others In obstructive lesions of the pancreatic duct and common bile duct, the secretin test helps to differentiate the location of the lesion and the degree of obstruction

Since stimulation of the vagus mechanism produces a juice rich in enzymes, while the secretin mechanism produces a juice rich in bicarbonate, the external secretion of the pancreas really serves two distinct functions namely neutralization and dilution, and the providing of enzymes important in digestion As Comfort points out, by using two different types of stimuli, that is, drugs which stimulate the vagus mechanism as one type and secretin as the other type, since each induces characteristic types of secretion it is possible to study separately the two functions of the external secretion of the pancreas Mecholyl, a parasympathomimetic drug, has been used by Bauman and others recently in a test for pancreatic function

Meyer and Necheles point out that in old people the salivary, gastric

creatitis the urinary test finds its greatest value, the amount being usually markedly increased Sometimes low urinary diastase values occur in cases of acute necrosis of the pancreas, but the test in general is a valuable aid in the diagnosis In chronic pancreatitis the urinary diastase may or may not be increased The unit of diastase selected by Wohlgemuth is the number of cubic centimeters of 0 1 per cent starch solution digested by 1 cubic centimeter of urine under standard conditions as to time, temperature and pH

Blood Amylase Clasen, *et al* report that experimentally the elevation of blood amylase after injury to the pancreas is only transient, and in chronic injury the blood amylase value is within normal range The normal range is fairly narrow, McCaughan states that if there is either an increase or a decrease amylase usually persists only for eight to fifteen days and then is likely to return to the normal range Hence there will be many negative results of the test in pancreatic tumors, cysts and ductal obstruction, its clinical value is greatest in acute conditions of the pancreas

Lewison gives the following evaluation of the serum amylase test Deviations of the serum amylase value from normal have been reported in many diseases other than pancreatitis, but there is a restricted range of deviation in such cases The amylase test is less reliable in the urine feces and duodenal contents than in the serum Diet and starvation have practically no effect on the serum amylase concentration Ligation or sudden obstruction of the pancreatic ducts cause a prompt marked rise later, pancreatic atrophy occurs and the serum amylase falls to below normal Complete pancreatectomy causes permanent lowering of the serum amylase to one third to one-half of normal The normal values have quite constant limits In liver diseases there are often depressed amylase levels In acute pancreatitis there is a quick rise to a peak in 48 hours followed by a return to normal in several days

Blood Lipase Zelikson found determination of the lipase content of the blood a better index of pancreatic disease than the amylase test. In acutely perforating peptic ulcers, Probstein, *et al* observed that the blood diastase level was above normal in cases in which the ulcer involved the pancreas whereas it was normal or subnormal in the cases in which the pancreas was not involved The fact that a high diastase value in the blood may signify either pancreatic disease or peptic ulcer perforating near the pancreas is of practical importance since the treatment required may be different The test can be used only to supplement the clinical findings

Symptoms of deficiency of the external secretion of the pancreas are

the pancreas has been removed, fed on a normal dog's diet and a maintenance dose of insulin, results in infiltration of the liver with fat and hypolipemia Lipotropic replacement (lipocaic, lecithin, choline raw pancreas) prevents these changes After excision of the pancreas in man, comparatively lower dosages of lipotropic substances seem to prevent this interference with liver function According to Dixon, *et al*, the human in whom the pancreas has been removed requires 20 to 70 units of insulin during the first week or so after operation, and 25 to 40 units daily for maintenance thereafter After total pancreatectomy there is considerable reduction in digestion and absorption of protein and fat About one-half of ingested fat and about one-third of ingested protein were lost in the feces Only one-third of the fat in the feces was neutral fat Absorption of calcium and phosphorus is adequate

Concentrated pancreatin is valuable in maintaining the nutrition of the patient although not a complete substitute for external pancreatic secretion

Reflux of Pancreatic Juice Schiller reports a case of fat necrosis in the liver cells caused by reflux of pancreatic juice in a patient having a fatty cirrhosis of the liver He points out that bile contains a small amount of amylase normally, therefore only high concentrations of amylase in the bile prove that pancreatic secretion is present in it On the other hand normal bile contains no lipase whatever, so that the presence of any lipase in the bile proves that reflux of pancreatic juice has occurred Of the three pancreatic enzymes, only lipase would be expected to produce visible microscopic changes in the liver following such reflux The effects of amylase on the liver cells cannot be observed histologically, trypsin can cause visible necrosis, but not unless it is first activated by enterokinase, and the bile does not contain this activator Lipase is easily activated by various substances, for example, by pure bile and by normal tissues, and therefore it can cause visible fat droplets because of fatty cirrhosis

PANCREATIC FUNCTION TESTS

Urinary Diastase· Wohlgemuth, in 1908, discovered a diastatic (starch splitting) ferment in the urine and described a method for its determination The diastase is absorbed from the alimentary tract into the blood stream and excreted by the kidneys The values obtained vary with the reaction of the urine, because every enzyme has an optimum pH the optimum for urinary diastase is 6 1 Diastase clings to urinary sediments, hence the urine must be well shaken before testing In renal disease the urinary diastase may be increased In acute pan-

Doubilet and Mulholland believe that spasm of the sphincter of Oddi is responsible for reflux of bile into the pancreas with resulting acute pancreatitis in at least 60 per cent of all cases of pancreatitis By means of cholangiographic and kymographic studies they have demonstrated this mechanism in human patients

Shumacker states that at least two per cent of all patients with severe acute pancreatitis later develop diabetes A much larger percentage of the surviving patients have milder grades of altered carbohydrate metabolism Probably mild cases of acute pancreatitis do not result in diabetes

V M Iovine, M.D

indefinite and because many pancreatic functions are performed also by other digestive organs, completely satisfactory specific functional tests are not available

A test proposed by Tremolieres estimates one constituent of pancreatic secretion, lipase, by measuring the rate at which ingested iodized oil is decomposed in the intestine, as determined by the rate of excretion of iodine in the urine' It is known that the iodine, once it is freed from the oil by digestion of the latter, is rapidly absorbed and excreted by the kidneys, hence it is assumed that the iodine elimination is proportional to the fat digestion In normal persons the amount of iodine eliminated in 24 hours is about 50 per cent of that which has been ingested It was found that when examination of feces indicated pancreatic insufficiency, the proportion of iodine excreted was always distinctly less than 50 per cent, usually from 20 to 30 per cent, but always more than 13 per cent and that in cases of combined pancreatic and hepatic dysfunction, still lower percentages of iodine excretion were found, ranging from 25 per cent down to even 3 per cent.

The severe general symptoms of acute hemorrhagic pancreatitis have been attributed by some to absorption of unaltered pancreatic juice into the blood stream from the peritoneal cavity Popper has shown that large amounts of amylase and lipase are demonstrable in the peritoneal exudate within an hour or two after the development of pancreatic edema produced in dogs by injections of bile or olive oil into the main pancreatic duct and subsequent ligation of the duct He observed that activated pancreatic juice diffuses first into the interstitial tissue of the gland and then into the peritoneal cavity In other experiments, Popper found that the intact intestinal wall is permeable to the pancreatic enzymes in complete duodenal obstruction The blood amylase gradually increased during the obstruction This was believed to be due to absorption from the bloody exudate which appeared early in the peritoneal cavity, for in cases of acute pancreatitis in man in which there is a large amount of peritoneal exudate, the concentration of amylase in the blood is higher than in cases with less exudate.

Ireneus found that injection of bile into the pancreatic duct sometimes produced acute edematous pancreatitis and on other occasions caused acute hemorrhagic pancreatitis, hence these two types of acute pancreatitis observed clinically are assumed to be stages in the same process The hemorrhagic exudate in animals with acute edema, hemorrhagic or necrosis of the pancreas was nontoxic when injected intraperitoneally in white mice and intravenously in dogs

production, beyond which the hourly output of hippuric acid must remain constant regardless of the amount of benzoic acid available Liver damage impairs glycine synthesis and so decreases the output of hippuric acid Synthesis of glycine is one function of the liver which appears to have practically no margin of safety In hepatitis, for example, there is a marked reduction in the excretion of hippuric acid out of all proportion to the amount of structural change in the liver

The hippuric acid excretion test is a measure of a protective mechanism. Quick believes that it largely overcomes the two serious objections levelled against every liver test, namely, that the reverse power of the liver is so great that impairment of function can be demonstrated only after extensive damage has occurred, and that the functions of the liver are so numerous that a test of any one of them fails to give reliable information concerning the state of the organ as a whole Boyce and McFetridge accept the test as an index of liver damage but regard it as inadequate as a guide for either diagnosis or treatment

The hippuric acid test is thought by Freeman and Grodins to be of greatest value in prognosis and in the estimation of surgical risk They consider it a reliable index of the degree of liver damage present. It is of some value in differentiating jaundice of intrahepatic origin from obstructive jaundice of short duration, but in long standing obstruction its value is limited Impairment of kidney function also limits the usefulness of the test.

Serum Phosphatase Freeman and Grodins have cited observations which tend to indicate that serum phosphatase elevation may be a much more sensitive indication of liver dysfunction than the serum bilirubin level, especially when there is insufficient impairment of function to be demonstrable by other means Elevation of serum phosphatase levels appears especially in obstructive jaundice and is useful in distinguishing obstructive jaundice from that originating in hepatocellular disease. Diseases of bone must be excluded There is experimental evidence that the enzyme may, in part at least, originate in the liver and not solely in the bone

Bromsulphthalene The determination of the degree of retention of bromsulphthalene dye injected into the blood stream is one of the most practical tests for liver damage of long standing in the absence of jaundice Although removal of the dye is probably performed by the whole reticuloendothelial system, dye retention apparently does not occur to any extent except in cases of failure of hepatic function with damage to that portion of the system found in the liver In the presence of jaundice satisfactory readings cannot be obtained It is not certain

Chapter XI

THE LIVER

Functions of the Liver. The liver performs many functions in the metabolism of the body, some of which are known, others, no doubt, remaining undiscovered The most important known functions, from the surgical standpoint, are 1 The formation of bile 2 The destruction and possible storage of red blood cells 3 The formation of fibrinogen, thrombin and other substances important in the coagulation of the blood 4 Fat metabolism 5 Protein metabolism with regulation of the level of plasma proteins The liver also plays a part in the metabolism and storage of carbohydrates and in the synthesis of antitoxins and other protective agents

Liver Function Tests The liver reserve is so great and its powers of regeneration are so unusual that function tests of all kinds are notoriously unreliable Although the van den Bergh reaction, levels of urobilinogen in the urine and stools, sugar tolerance tests performed with levulose and galactose, the hippuric acid excretion test and others have been used successfully in the past, none of them gives an accurate picture of liver potential The best dye retention test is probably the determination of bromsulphthalene retention One of the best indices of liver function can be found in the response of a lowered prothrombin level to the administration of vitamin K

Extirpation of the liver results in hypoglycemia and jaundice The jaundice develops after six hours due to the retention of bile pigments in the blood stream Very little of this pigment is derived from the spleen or other abdominal viscera, most of it originating in the bone marrow After liver extirpation the blood van den Bergh reaction is "indirectly positive" at first and then becomes biphasic There is no change in the cholesterol content of the blood

Hippuric Acid Test Quick's hippuric acid test of liver function makes use of the best known of the conjugation mechanisms of detoxification, namely, the joining of glycine to benzoic acid in order to obviate the toxic effect of the latter This synthesis, resulting in the formation of hippuric acid, is primarily a function of the kidney, but the required glycine is formed only in the liver Therefore, the rate of synthesis of hippuric acid depends upon the rate at which the liver supplies glycine, and there is a definite maximum capacity for glycine

present, and it is impractical clinically because the required intra venous injection causes local thrombosis in a large proportion of cases

Bile Acids and Bile Salts The bile acids (taurocholic and glycocholic) and their salts, unlike the bile pigments, perform a number of functions in the process of nutrition They are not excreted from the body but are passed into the intestinal tract in the bile, from which they are reabsorbed into the blood stream, returned to the liver and re secreted by the latter None appears in the feces or urine A high protein diet increases and carbohydrate decreases the formation of bile salts Fetal bile contains little or no bile salts The bile salts help to keep the cholesterol of the bile in solution, facilitate the digestive ac tions of all the pancreatic enzymes, assist in the absorption of the prod ucts of fat cleavage and in the absorption of vitamin K from the intes tinal tract, aid in the absorption of secretin, and stimulate the liver to produce bile

When bile salts fail to enter the intestine, 25 to 75 per cent of in gested fat is lost in the feces, most of it as fatty acids and soaps, but some as neutral fat. Absence of bile decreases the absorption of fatty acids and soaps more than it impairs the digestion of fats The un absorbed fatty acids are responsible for the characteristic rancid odor of acholic stools The clay color of the latter is due in part to lack of bile pigments, but in part also to excess of fat Acholic stools usually contain fewer bacteria than normal ones The presence of bile salts in the intestine causes stimulation of the secretory activity of the liver, though by what mechanism it is unknown

Bile acids are known to be produced, concentrated and destroyed only in and by the liver Ravdin has shown that they are always absent from the hepatic bile after the common duct has been completely ob structed for a week or more They reappear only very slowly after release of the obstruction Hepatic damage is always accompanied by a low concentration of bile acids, as demonstrated by Grey and his coworkers Grey estimated the hepatic damage from the history, function tests and gross appearance of the liver at operation These workers also found a postoperative depression of the function of concentrating the bile acids, recovery from this depression occurred rapidly if the liver was normal but slowly if the liver was damaged

When stones are present in the gallbladder there is a consistent and striking decrease in the concentration of bile salts in the bile Crandall and Ivy have pointed out that since the bile salts are essential for the solution of all lipids in bile, including cholesterol, their decreased con centration in the presence of stones strongly suggests that the precipi

per cent protein and not more than 5 per cent fat, containing 2500 to 3500 calories Such a diet cannot be given by the parenteral route but requires oral administration, at least in part

Liver Failure: Boyce and his co-workers suggest the following explanation for "liver death" It is assumed that in every case there is some liver damage present preoperatively but it is not too severe to be compatible with the strain of ordinary life Following surgical operations, the damaged liver is unable to perform its functions adequately and permits toxic substances normally found in the intestinal tract to pass through into the general circulation undetoxified These substances, together with additional toxic products discharged from necrotic liver cells, impinge upon the kidneys, which are forced to take on the detoxifying function native to the liver, but have only a slight margin of safety for that work and fail to accomplish it

THE BILE

Bile is alkaline in reaction, due principally to the sodium carbonate which it contains Its most important components are bile pigments, bile salts and cholesterol

Bile Pigments: The bile pigments are bilirubin and biliverdin The latter is merely an oxidation product of the former Bilirubin is manufactured from the hemoglobin of broken-down red cells, not by the liver cells, but in the circulating blood stream by the reticulo-endothelial system. The bilirubin is then removed from the blood plasma by liver cells and excreted into the bile passages to be eliminated from the body, for it serves no physiological function During its passage through the intestinal tract, the bilirubin is converted to urobilin by the action of bacteria This conversion occurs chiefly in the large bowel and hence the urobilin is excreted in the feces It is partly absorbable, however, so that some of it is reabsorbed from the colon into the blood stream and carried by the latter to all parts of the body including the liver Thus, a portion of the pigment which is excreted by the liver as bilirubin is ultimately returned to it in the form of urobilin, the remainder leaves the body in the feces Most of the reabsorbed urobilin is excreted by the kidneys in the urine in the form of a precursor, urobilinogen The small fraction recovered by the liver is believed to be used in the formation of new hemoglobin Bile pigment in some unknown manner can facilitate either iron absorption or iron utilization In certain types of anemia bile pigment can be reabsorbed from the gastrointestinal tract for the building of hemoglobin Bilirubin clearance is one of the most sensitive tests of liver function, but it is valueless if jaundice is

amount in the bile increases to two or three times the normal Most of the cholesterol in the bile is reabsorbed in the intestines, indicating that it is of some physiological use A small fraction is excreted in the feces

Rousselot and Bauman placed a solution of cholesterol and conjugated bile salts into the gallbladder Within 24 hours there was a loss of 50 per cent of the cholesterol and a gross lesion of the gallbladder was produced, closely resembling human cholesterosis They, therefore, suggested that the gallbladder wall absorbed cholesterol from the bile contained within its lumen

According to Wilkie and Doubilet, the amount of cholesterol passing through the mucosa of the gallbladder and the direction of its passage depends upon the blood bile cholesterol ratio On tying the cystic duct they found that cholesterol passed from the blood into bile, if the cholesterol concentration of the bile was lower than that of the blood and vice versa

The cholesterol content of the blood in obstructive jaundice is increased from 0 25 to 0 7 per cent because of the reabsorption of bile into the blood from the bile capillaries of the liver In the absence of jaundice, there usually is no change in the concentration of blood cholesterol in the presence of gallstones Cholesterol is said to increase in the blood after splenectomy for hemolytic jaundice, however, and may be responsible for the decrease in hemolysis In normal health free cholesterol amounts to approximately 26 9 per cent of the total cholesterol in the blood serum Pickhard and his co-workers felt that changes in the ratio between free and total cholesterol offer a much more significant indication of liver function than changes in the total cholesterol alone Changes in the ratio seem to measure a reversible function of the liver, namely, the esterification of the cholesterol with the higher fatty acids, and its opposite the hydrolysis of the cholesterol esters by means of esterases An elevation in the percentage of free cholesterol in relation to the ester-cholesterol faction is taken to indicate a lowering of the liver's functional reserve and a poor operative risk In cases studied by Pickhard *et al* free cholesterol values varied from 31 to 110 milligrams The total cholesterol varied from 180 to 220 milligrams per hundred cubic centimeters of serum

Control of Bile Secretion The output of bile in 24 hours is normally approximately 500 to 1000 cubic centimeters Bile is secreted continuously, independent of the nerve supply of the liver, at a [illegible] rate under a low pressure of approximately 30 centimeters of bile Because of this low pressure its flow can be checked [illegible] by obstruction

tation of fatty acids and cholesterol may occur secondary to the decrease in bile salt concentration These authors have also pointed out that since the only value of bile in the digestive tract, according to all information, lies in its bile salt content, and since the bile salt concentration in the drainage bile obtained through a common duct tube may be negligible, it seems far more beneficial to administer exogenous bile salts by mouth in the maximum dosage tolerated than to readminister the bile itself by mouth Hawkins and Whipple, in 1935, demonstrated that in dogs with biliary fistulae, unless bile is given by mouth, cholelithiasis may occur This effect may well be due to decreased bile salt concentration as a result of prolonged drainage

Bile is essential to life Animals with continuous biliary fistulae die unless bile is returned to the gastrointestinal tract Hawkins and Whipple ascribed it to deprivation of some constituent of bile elaborated by the liver Boyd and his associates ascribed it to loss of inorganic salts of the body which increases with the age of the fistula Since bile salts are necessary for the absorption of vitamin D and vitamin K, their lack may produce osteoporosis and prothrombin deficiency Although they are necessary for the absorption of carotene, a precursor of vitamin A, they are not necessary for the absorption of vitamin A itself

Because of the important functions of bile, many sequellae follow the formation of biliary fistulae Some of these are stone formation due to inhibition of fat absorption, osteoporosis due to inadequate absorption of vitamin D, duodenal ulcer due to lack of the neutralizing effect of bile on gastric juice and purpura and hemorrhage due to lack of vitamin K Crandall and Ivy have pointed out that in biliary obstruction, which is more common than fistula formation, the resulting disturbance is even more complex for there are, in addition to the complications of biliary fistulas, disorders of many other liver functions due to back pressure or infection The liver is probably the site of the formation of ketone bodies in diabetes In experimental diabetes, however, hypophysectomy diminishes or abolishes the excretion of ketone bodies

Cholesterol. Cholesterol, although a fat-like substance (lipoid) in many of its physical and chemical properties, is not a fat but a higher alcohol Normally present in the blood and bile in a concentration of about 0 15 to 0 2 per cent, its concentration is increased in pregnancy and in lipemia from various causes such as diabetes and starvation The concentration of cholesterol in the bile generally varies directly with that in the blood In pregnancy, however, the cholesterol content of the bile is low, while that of the blood is high, after parturition the

amount in the bile increases to two or three times the normal Most of the cholesterol in the bile is reabsorbed in the intestines, indicating that it is of some physiological use A small fraction is excreted in the feces

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The production of bile is subject to both nervous and chemical control The vagus appears to be a true secretory nerve to the liver but is capable of increasing the flow of bile only slightly No sympathetic secretory innervation of the liver has been demonstrated Although secretin, which stimulates pancreatic secretion, has a slightly accelerating effect on the production of bile, the bile salts, especially those of taurocholic acid, are the most powerful stimulus for bile formation After the intake of food there is an increased flow, brought about probably by means of both the nervous (vagus) and chemical (secretin reinforced by the action of bile salts absorbed from the intestines) mechanisms Bile secretion is temporarily inhibited by general anesthesia and by trauma Although complete blockage of the bile passages results in a few months of loss of health, followed ultimately by death, it has been shown that almost complete obstruction (80 to 90 per cent) can be tolerated by the dog with normal health for long periods of time

Carbohydrate and protein metabolism in the liver are regulated by autonomic impulses from the diencephalon by way of both the vagus and the sympathetic (fifth and sixth thoracic segments) systems The sympathetic system augments and the parasympathetic (vagus) inhibits the chemical processes

Bile Peritonitis· In bile peritonitis local injury to the peritoneum by irritating bile salts occurs, sometimes followed by bacterial peritonitis if infection of the biliary tract is present The loss of bile into the peritoneal cavity also produces dehydration and its reabsorption into the blood stream results in jaundice From experiments on dogs, Manson and Eginton infer that death in bile peritonitis may be due to the chemical peritonitis and dehydration rather than to the effects of bile absorption or infection

THE GALLBLADDER AND BILE DUCTS

Motor Activity of the Gallbladder and Bile Ducts The gallbladder is subject to two types of contractions—first, slow, rather weak contractions at somewhat irregular intervals, and, second, tonic contractions of the musculature of the organ as a whole These contractions are effected by both chemical and nervous influences Morphine inhibits its muscular activity, adrenalin induces strong contractions, while vagus stimulation has no apparent effect The expulsive power of the normal gallbladder is approximately 300 millimeters of bile pressure, but it is never greater than the secretory pressure of the liver, which is about 25 millimeters of mercury

The most effective stimulus for contraction of the gallbladder is the

presence of fat in the intestines This action is probably produced by means of absorbed products of fat digestion The presence of fat in the intestines causes complete emptying of the gallbladder, no other stimulus is capable of producing this The effect is produced even after denervation of the organ Protein produces a much less effective contraction and no contraction whatever is induced by hydrochloric acid, secretin or bile salts

The sphincter of Oddi prevents a continuous discharge of bile from the common duct and is able normally to stand a pressure of 300 millimeters of bile during the fasting state During digestion, however, it yields at a pressure of about 100 millimeters of bile

Cholecystokinin Cholecystokinin, produced in the duodenum and upper jejunal mucosa, is the most powerful hormonal stimulus of gallbladder contraction Formation of this hormone is produced differently by different types of foods Fats, particularly egg yolk and cream, are the most effective substances Animal proteins are the next most effective, carbohydrates have no effect at all Cholecystokinin seems to have no other effect in the body than the stimulation of powerful gallbladder contractions This effect is not abolished by atropine, which normally relaxes the gallbladder

Marrazzi observed the gallbladder in an anesthetized, trained dog by means of abdominal endoscopy He found that during a period when the gallbladder is emptying no muscular contractions could be observed Emptying of the gallbladder apparently was not produced or influenced by drugs which have a definite effect on smooth muscle activity, including cholecystokinin or mechanical and electrical stimuli These observations suggested that in dogs muscular contraction in any way comparable to that occurring in other hollow organs plays little or no part in the emptying of the gallbladder In the fish muscular activity has been shown very convincingly to play an important role in gallbladder emptying There is a striking, progressive diminution in visible gallbladder activity from the lower to the higher animals

The Sphincter of Oddi The functions of the sphincter of Oddi are to aid the filling of the gallbladder, to prevent regurgitation of the duodenal contents into the common duct and to serve as a barrier against ascending infection and cholangitis According to Ivy and Bergh, the sphincter can sometimes resist pressures up to 750 millimeters of bile, under certain conditions Hence by spasm it can prevent gallbladder emptying After removal of the gallbladder, the sphincter of Oddi becomes incompetent indicating a close functional relationship between the two structures Later, however, it becomes competent again

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Bile Peritonitis In bile peritonitis local injury to the peritoneum by irritating bile salts occurs, sometimes followed by bacterial peritonitis if infection of the biliary tract is present The loss of bile into the peritoneal cavity also produces dehydration and its reabsorption into the blood stream results in jaundice From experiments on dogs, Manson and Eginton infer that death in bile peritonitis may be due to the chemical peritonitis and dehydration rather than to the effects of bile absorption or infection

THE GALLBLADDER AND BILE DUCTS

Motor Activity of the Gallbladder and Bile Ducts The gallbladder is subject to two types of contractions—first, slow, rather weak contractions at somewhat irregular intervals, and, second, tonic contractions of the musculature of the organ as a whole These contractions are effected by both chemical and nervous influences Morphine inhibits its muscular activity, adrenalin induces strong contractions, while vagus stimulation has no apparent effect The expulsive power of the normal gallbladder is approximately 300 millimeters of bile pressure, but it is never greater than the secretory pressure of the liver, which is about 25 millimeters of mercury

The most effective stimulus for contraction of the gallbladder is the

presence of fat in the intestines This action is probably produced by means of absorbed products of fat digestion The presence of fat in the intestines causes complete emptying of the gallbladder, no other stimulus is capable of producing this The effect is produced even after denervation of the organ Protein produces a much less effective contraction and no contraction whatever is induced by hydrochloric acid, secretin or bile salts

The sphincter of Oddi prevents a continuous discharge of bile from the common duct and is able normally to stand a pressure of 300 millimeters of bile during the fasting state During digestion, however, it yields at a pressure of about 100 millimeters of bile

Cholecystokinin Cholecystokinin, produced in the duodenum and upper jejunal mucosa, is the most powerful hormonal stimulus of gallbladder contraction Formation of this hormone is produced differently by different types of foods Fats, particularly egg yolk and cream, are the most effective substances Animal proteins are the next most effective, carbohydrates have no effect at all Cholecystokinin seems to have no other effect in the body than the stimulation of powerful gallbladder contractions This effect is not abolished by atropine, which normally relaxes the gallbladder

Marrazzi observed the gallbladder in an anesthetized, trained dog by means of abdominal endoscopy He found that during a period when the gallbladder is emptying no muscular contractions could be observed Emptying of the gallbladder apparently was not produced or influenced by drugs which have a definite effect on smooth muscle activity, including cholecystokinin or mechanical and electrical stimuli These observations suggested that in dogs muscular contraction in any way comparable to that occurring in other hollow organs plays little or no part in the emptying of the gallbladder In the fish muscular activity has been shown very convincingly to play an important role in gallbladder emptying There is a striking, progressive diminution in visible gallbladder activity from the lower to the higher animals

The Sphincter of Oddi The functions of the sphincter of Oddi are to aid the filling of the gallbladder, to prevent regurgitation of the duodenal contents into the common duct and to serve as a barrier against ascending infection and cholangitis According to Ivy and Bergh, the sphincter can sometimes resist pressures up to 750 millimeters of bile, under certain conditions Hence by spasm it can prevent gallbladder emptying After removal of the gallbladder, the sphincter of Oddi becomes incompetent indicating a close functional relationship between the two structures Later however it becomes competent again

and even overactive so as to cause dilatation of the bile ducts This sequence of changes may account for the temporary relief of symptoms with their later recurrence, often observed after cholecystectomy In such cases the sphincter may be hypertonic or hypertrophic before operation Boyden found three different types of gallbladder response to ingestion of a fat meal in normal human subjects depending upon the relative degree of activity induced in the gallbladder itself and in the sphincter of Oddi

Since motor dysfunctions of the biliary tract vary and cannot be divided into clearly defined entities, therapeutic indications are quite confused Recommendations of the most favorable type of diet tend in general toward a low fat intake Ivy and Bergh, however, for prevention of gallbladder disease, advise inducing daily evacuation of the viscus by "the appropriate intake of fat" They recommend this particularly in antipartum care They believe that the amount of fat given for hypertonicity of the sphincter will depend upon the condition of the gallbladder If the gallbladder is atonic, more fat should be given, if irritable the fat intake should be adjusted to the "tolerance" of the patient This tolerance can be ascertained after careful dietary experimentation They believe that too much fat will irritate the gallbladder, but absence of such an excitant factor may cause stasis and stasis should be avoided

Bauer *et al* found that in severe attacks of biliary colic the pain will promptly be relieved by the very slow, intravenous administration of 20 cubic centimeters of a 5 per cent solution of calcium chloride This procedure may be of value not only in treatment but in diagnosis, since its failure to relieve pain may signify an inflammatory lesion rather than simple spasm of smooth muscle

Improved anatomical methods have shown the great complexity of the structure of the sphincter of Oddi Bergh and Layne measured simultaneously the pressure and rate of flow of bile in the common duct and the pressure in the duodenum following sudden distention of the common duct in patients upon whom cholecystectomy and choledochostomy had been performed As a result of these experiments they concluded that the sphincter can act independently of the duodenal musculature and that the pain produced by sudden distention of the common bile duct can be correlated only with spasm of the sphincter

Effect of Drugs on the Sphincter of Oddi Layne and Bergh found that amyl nitrite and nitroglycerin relieved the sphincter spasm thus induced, while atropine and pilocarpine did not Morphine and other opium preparations induced spasm of the sphincter of Oddi Ingestion

of a fatty meal caused contraction of the gallbladder and relaxation of the sphincter region, but there did not seem to be a fixed reciprocal relationship between these two responses Each response apparently was an independent reaction to the same stimulus Reich has proposed denervation of the common duct as a means of relieving spasm of the sphincter of Oddi permanently, but there is no evidence that autonomic nerve fibers exert any significant influence over this sphincter in man

Doubilet and Mulholland have suggested division of the sphincter of Oddi to prevent spasm with reflux bile flow into the pancreatic duct They found that the musculature of the overlying duodenal wall is sufficient to control the flow of bile and pancreatic secretions

FUNCTIONS OF THE GALLBLADDER

Absorption The normal gallbladder absorbs water, chloride and bicarbonate rapidly As a result of this selective absorption, the bile is rendered more acid and the hepatic bile is concentrated four to 10 times Thus, the gallbladder's reservoir function is much greater than the size of the organ would indicate In the fasting state the human gallbladder is capable of storing the entire 12 to 24 hour output of hepatic bile If a dog's common duct is ligated and the gallbladder removed in the same operation, jaundice begins to appear in three to six hours If the common duct is ligated and the gallbladder not disturbed jaundice does not appear for 36 to 48 hours Absorption of water by the gallbladder prevents an excessive rise in intracystic pressure Its absorptive capacity also makes possible cholecystography by the Graham Cole method This concentrating activity is not disturbed by cholesterosis and the latter does not interfere with the emptying of the gallbladder unless there are associated inflammatory changes

Secretion The gallbladder normally secretes a mucoid fluid In complete gallbladder fistula in man 20 cubic centimeters per 24 hours have been collected

Under certain conditions the liver secretes a colorless, watery substance called 'white bile,' which contains large amounts of calcium carbonate and almost no bile salts and bile pigments Although no adequate explanation has been found for its function, white bile is frequently seen in the following conditions 1 Common duct obstruction with a functionless gallbladder 2 Partial obstruction in which the liver secretes bile against pressure 3 Severe, ascending infections of the biliary tract 4 Toxic hepatitis

In chronic cholecystitis there is a decrease in the concentration of calcium and bile salts in the bile and an increase in chloride These

and even overactive so as to cause dilatation of the bile ducts This sequence of changes may account for the temporary relief of symptoms with their later recurrence, often observed after cholecystectomy In such cases the sphincter may be hypertonic or hypertrophic before operation Boyden found three different types of gallbladder response to ingestion of a fat meal in normal human subjects depending upon the relative degree of activity induced in the gallbladder itself and in the sphincter of Oddi

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obstruction and the reappearance of the bile salts is proportional to the degree of cholangitis associated with the obstruction and the length of the interval may serve as an indication of the rate of return of normal liver activity In biliary fistulas with diversion of bile from the intestinal tract, the loss of bile salts is more important than the loss of base or chloride

Zollinger distended the gallbladder and common bile duct in man by means of a sterile rubber balloon Pain was referred to the epigastrium in both cases, that from the common duct being more severe The pain was not referred to the right upper quadrant in either case, but respiratory distress was produced in both instances Distention of the common duct induced vomiting, whereas distention of the gallbladder did not.

According to Graham and Mackey in cases of cholecystitis without stones, when severe pain is absent, the results of cholecystectomy are likely to be unsatisfactory in about 40 per cent of cases That is, symptoms other than pain commonly associated with gallbladder disease are much less likely to disappear after cholecystectomy than is pain itself unless the pathological changes in the gallbladder are definite and marked or stones are present They suggest that such patients may be suffering from conditions which are on the borderline between purely functional disorders and actual anatomical changes Even though some are anatomical changes it may be that their symptoms are not due to these minor changes but to a functional disorder accompanying them Fifteen days after the removal of the gallbladder in dogs Sutton found that striking changes in the epithelium of the intrahepatic bile ducts begin These changes are complete after 40 days The normal low columnar epithelium of the duct is transformed into a high columnar type and projecting folds develop so that the mucosa resembles that of a normal gallbladder Likewise in man he found that following cholecystectomy either functional or operative mucosal folds and villi appear in the intrahepatic bile ducts similar to those present in the normal gallbladder He concluded that the intrahepatic bile ducts appear to adapt themselves to perform functions of the gallbladder following destruction of the latter

Lavage of the duodenum with 33 per cent magnesium sulfate, as suggested by Lyon and by Meltzer as a means of draining the gall bladder, does not cause any contractions of the gallbladder detectable by x ray It is probable that ingestion of the solution would be as effective as administration by tube and also that ingestion of fat would probably be more effective.

changes increase with increasing severity of gallbladder damage as measured by cholecystograms. The cholesterol concentration tends to vary in the same manner as the bile salt concentration, but its variation is not consistent and there are many exceptions

Since bile salts aid in keeping cholesterol in solution, studies have been made to determine whether a change in the bile salt-cholesterol concentration ratio in the bile is a factor in cholesterol precipitation and, therefore, in gallstone formation In studying the chemistry of human gallbladder bile removed at operation, Ravdin found that stones of different chemical composition occur in bile of very similar character, and stones of the same type are often found in bile of different chemical compositions It was recognized, of course, that the stones found were not necessarily formed under the conditions of the bile found at operation Man is the only animal in whom cholesterol stones are common Lloyd mentioned four different opinions regarding the activity of the gallbladder in relation to biliary cholesterol 1 The gallbladder absorbs cholesterol 2 It secretes cholesterol 3 It concentrates cholesterol to an equal degree as the other biliary constituents 4 It varies these activities according to the relative concentrations of cholesterol in the blood and bile In studying the bile in 31 cases at postmortem, he found that in 19 cases the bilirubin and cholesterol concentrations were approximately equal, in eight cases, the bilirubin concentration was greater (cholesterol absorbed?) and in four cases the bilirubin concentration was less (cholesterol secreted?)

The wide variations in bilirubin and cholesterol concentration in both the hepatic and gallbladder bile are shown by the following figures

	Bilirubin	*Cholesterol*
Hepatic bile, milligrams per 100 cc	96 to 1720	0 25 to 13 3
Gallbladder bile, milligrams per 100 cc	96 to 6000	0 8 to 17 85
Concentration ratio	0 96 to 24 5	0 6 to 36 1

The extreme variations in hepatic bile point to great flexibility in the excreting power of the liver, the wide range of concentration ratios indicates a remarkable flexibility of gallbladder function (concentrating power) Lloyd concludes from these observations that, in most cases, both bilirubin and cholesterol are concentrated to an equal degree by the gallbladder, but that in some cases cholesterol may be either added to or removed from the gallbladder bile as Wilkie and Doubilet (1933) have postulated

There is marked reduction in concentration or even absence of bile salts obtained by common duct drainage after release of a common duct obstruction (Ravdin *et al*) The interval between the release of

creatitis Popper studied 16 cases of acute pancreatitis and found pancreatic ferments present in the bile passages in all instances He found the presence of bile in the pancreatic duct only exceptionally at autopsies on patients who died of acute pancreatitis

Gallstones The majority of gallstones contain about 86 per cent cholesterol If cholesterol crystals or bile pigment granules are found on microscopic examination of the bile obtained by drainage of the duodenum, the presence of gallstones is almost certainly indicated This is true regardless of whether the bile is of the concentrated (gallbladder bile) or unconcentrated (liver bile) type Likewise, the absence of cholesterol crystals or bile pigment granules from concentrated bile is fairly strong evidence against the presence of stones Their absence from unconcentrated bile is not conclusive evidence of the absence of pathological changes in the gallbladder or the absence of stones Bile pigment granules are seen much less frequently than cholesterol crystals If pigment granules alone are found in considerable quantity, pure pigment stones may be suspected Such stones, which are uncommon, form only two or three per cent of all gallstones, but may occur without apparent chemical or microscopic change in the gallbladder bile obtained at operation

Gallstones usually composed almost entirely of pigment occur in about 60 per cent of patients with congenital or acquired hemolytic jaundice In such cases the pigment is present in the bile in great excess Brooks reported stones in a patient four years old with congenital icterus In a similar case reported by Hurley and Moore, after splenectomy the stones seemed to have disappeared almost entirely as far as could be determined by x ray examination

The preponderance of experimental proof indicates that the gallbladder absorbs cholesterol from the bile, cholesterosis probably being an infiltrative process When the concentration of cholesterol esters in the gallbladder bile is abnormally increased, absorption of these substances may lead to their deposition in the wall of the gallbladder In such a case the lipoid is stored principally in the endothelial cells of the lymphatics of the submucosa

Although it is a common practice to forbid the intake of fats to patients with gallbladder disease, no one has been able to produce gallstones in man by feeding diets high in cholesterol Despite evident clinical benefit often obtained by the avoiding of fats, the conclusion seems warranted that there is no wholly logical diet for cholelithiasis or cholecystitis Although it is commonly assumed that common duct stones in most instances originate in the gallbladder, Carter *et al* noted

Gallbladder bile differs from bile freshly secreted by the liver in that it is six to 10 times more concentrated and contains mucin Bile as secreted by the liver contains fixed base and chloride in about the same concentrations as plasma and is alkaline in reaction Gallbladder bile contains about twice as much base as liver bile but almost no chloride If the missing chloride were replaced by bicarbonate the gallbladder bile would be much more alkaline than liver bile, but this is not the case for it is neutral or even slightly acid Therefore, the chloride must not be replaced by bicarbonate but by some other acid radicals, presumably bile acids Thus it seems that for digestion in the upper part of the intestine large amounts of fixed base are needed more than chlorides Gallbladder bile can supply this base quickly when needed without necessitating any sudden withdrawal of base from the blood plasma The gallbladder thus protects plasma base from sudden depletion In this respect it is a more advantageous source of base than pancreatic juice, for the pancreas can supply base only by removing it directly from the plasma as needed (Gamble and McIver, 1928)

Cholecystography. Although the gallbladder excretes certain substances, notably bacteria, from the blood into its lumen, the dye administered for cholecystography is not excreted by the gallbladder wall but is excreted by the liver cells into the bile in a weak concentration and becomes concentrated following absorption of water by the gallbladder mucosa Once the dye is absorbed into the blood stream its failure to delineate the gallbladder indicates occlusion of a cystic duct, sclerosis of the gallbladder, or disease of the gallbladder wall impairing its power to absorb water. Sixty to 70 per cent of the dye is excreted by the liver The colon excretes about 25 per cent and the kidneys 5 to 10 per cent Toxins which are excreted by the liver become concentrated in the gallbladder by reabsorption of water in the same manner as the dye

Bile obtained from the gallbladder at operation contains pancreatic ferments in about 15 per cent of cases Bile obtained from the common duct by choledochostomy contains amylase in about 30 per cent of cases The presence of these pancreatic ferments in the bile is not necessarily abnormal in itself for it occurs in some instances in which the gallbladder and bile ducts are normal Colp and Doubilet have demonstrated the presence of pancreatic ferments in the draining bile in a case in which there was rapid digestion of the skin around a biliary fistula If the presence of pancreatic ferments in the bile passages is due to obstruction at the ampulla of Vater, however, the prevention of discharge of pancreatic trypsin predisposes to acute pan-

some time has elapsed (delayed direct reaction) or only after the preliminary addition to it of another substance, namely alcohol (indirect reaction) The delayed direct and indirect reactions have the same significance, namely, they identify prehepatic ("R E") bilirubin

Another difference between pre- and posthepatic bilirubin is the fact that prehepatic bilirubin is not excreted by the kidney probably because it exists in combination with protein in a colloid state, whereas posthepatic bilirubin, having been dissociated from protein by the liver cells and being crystalloid in character, is more permeable and is readily excreted by the kidney In jaundice due to excess of prehepatic bilirubin, therefore, the urine does not contain bile (acholuric jaundice), in jaundice due to the presence of posthepatic bilirubin in the blood, the urine does contain bile In jaundice with bilirubin in the urine the van den Bergh immediate direct reaction is always obtained and in jaundice with no bilirubin in the urine the van den Bergh indirect reaction is obtained Therefore, examination of the urine for bilirubin gives the same information as the van den Bergh test, and is easier to perform

JAUNDICE

Etiology and Classification of Jaundice Jaundice is due to an excessive amount of bilirubin of either kind (pre- or posthepatic) in the blood tissues Three types of jaundice occur

1 *Hemolytic jaundice* (acholuric, dissociated) is due to abnormally increased destruction of red cells and to excessive production of bilirubin by the reticulo-endothelial system The red cell destruction may be primary, or it may be the result of overactivity of the endothelial system Clinically some liver damage is always found in this type (See type 3 below)

2 *Toxic or infectious jaundice* is due to accumulation of the normally formed prehepatic bilirubin in the blood because it is not extracted by the liver at the normal rate by reason of some disturbance of the liver cells from toxemia, infection or other cause This type, too, rarely occurs in pure form

3 *Obstructive jaundice* is due to reflux of posthepatic bilirubin from the bile passages into the lymphatic or blood vessels of the liver, because of gross or microscopic obstruction of the biliary passages or destruction of some of the liver cells which normally separate th[illegible] and bile channels Cholangitis may cause obstructive jaundice [illegible]ing the smaller radicals of the hepatic duct with exudate.

[illegible]prehepatic) jaundice, the liver cells may [illegible]

that in the majority of cases the structures of stones from the gallbladder and common duct are different From a study of clinical cases by means of chemical and microscopic analysis of gallbladder and common duct bile at operation and through postoperative drainage tubes, they have concluded that the origin of common duct lithiasis is as follows The gallbladder becomes diseased first and with the passage of time it becomes obliterated and functionless, while the common duct takes over the concentrating power of the gallbladder to a greater or lesser degree This is evidenced by increased concentration of bile in the common ducts of patients with advanced gallbladder disease The concentration of the bile in the common duct is further increased by stasis, stasis predisposes to infection, and this combination of factors causes the formation of calcium bilirubinate stones They, therefore, infer that common duct stone formation, thought to be related to preexisting chronic cholecystitis, represents a separate and distinct pathological process which cholecystectomy may fail to arrest

Calculi have been produced experimentally in the bile ducts, the kidney and the urinary bladder of animals fed a diet deficient in vitamin D Saiki has reported that a patient receiving a diet deficient in vitamin D developed late rickets complicated by a gallstone and that the gallstone was dissolved in vivo by adding an adequate amount of vitamin D to the diet

Bisgard and Baker hold that most cases of acute gangrenous cholecystitis are caused by the reflux of pancreatic enzymes into the gallbladder

RETICULO-ENDOTHELIAL FUNCTIONS OF THE LIVER

Van den Bergh Reaction Normally this extrahepatic reticulo-endothelial ("R-E") bilirubin is extracted from the blood by the liver cells and discharged into the bile capillaries with the bile In this process, however, the liver cells do not act merely as conveyors, for they alter the bilirubin chemically in some manner as it passes through them The change produced consists of the transformation of the bilirubin from a colloid to a crystalloid state by the removal from it of a protein molecule This altered or "liver" bilirubin found in the bile readily and promptly yields a violet color with the reagents used in the van den Bergh test (immediate direct reaction) This identifies it as bilirubin which the liver cells have acted upon The "R-E" bilirubin which has not yet passed through the liver cells is more resistant to the same van den Bergh reagents, and yields the color change only after

of the enzyme in bone, especially growing bone Hence, one would expect that with the formation of callus in the process of fracture repair there would be a local increase in phosphatase activity Experimentally, such a local increase at the site of fracture is found The concentration of phosphatase in the blood serum, however, is not consistently elevated in fractures and is no index of the healing rate, according to Mitchell's observations in 75 clinical cases Mitchell states that though there is often a slight increase in serum phosphatase, it seems that it is secondary to the local increase and not vice versa There is, correspondingly, no significant change in the phosphorus concentration in the blood after fractures Hunsberger and Ferguson, contrary to Mitchell's report, found that in cases of fracture the serum phosphatase increased progressively, and that there was an inverse relationship between the concentration in the serum of the inorganic phosphorus and the serum phosphatase In generalized bone diseases they found the serum phosphatase increased

Armstrong *et al*, found that after experimental obstruction of the common bile duct in dogs the serum phosphatase rose to progressively higher values each day, reaching from 30 to 100 times the initial concentration after six days When the obstruction was relieved, the serum phosphatase fell to the original value Feces from dogs both before and after obstruction possessed great phosphatase activity Armstrong and his co-workers observed that gallbladder bile contains large amounts of phosphatase, while bile from a fistula contains even greater amounts In clinical cases of proved obstructive jaundice, they found that the serum phosphatase increased from day to day during the development of jaundice and diminished during the subsidence of the jaundice The height to which the phosphatase activity rose was considerably less than that attained in dogs In two cases of latent hemolytic jaundice in man which were studied, no appreciable rise in serum phosphatase occurred

Obstructive jaundice can be recognized by the increased phosphatase activity in the blood, which rises to above 10 units only in this type As Rothman *et al* point out, a quantitative bilirubin estimation must be made at the same time as the phosphatase determination because of the observation that in obstructive jaundice the rise in phosphatase tends to run parallel with the rise in serum bilirubin until the limits of the phosphatase values are reached In nonobstructive jaundice on the contrary in spite of the progressive increase in serum bilirubin the phosphatase values do not run parallel and rarely rise above 10 units The differentiation of the two types of jaundice therefore, depends

an excessive amount of viscid posthepatic bilirubin into the bile capillaries that it blocks some of these and adds an element of obstructive jaundice (crystalloid bilirubin) to the already existent hemolytic type Similarly in toxic (prehepatic) jaundice, if the intoxication of the liver advances to the stage of actual necrosis of some of the liver cells the loss of the barrier between blood and bile channels results in some degree of "reflux" obstructive jaundice

Because of the overlapping of these etiologic types of jaundice in individual patients, the following classification, proposed by Rich, is preferable This classification is based on pathogenesis and corresponds well with the clinical grouping of cases

1 *Retention jaundice Cause* Overproduction of bilirubin plus subnormal liver function

2 *Regurgitation jaundice Cause* Rupture of canaliculi due to (a) necrosis of liver cells, and (b) obstruction of bile channels

3 Unknown group (e g , *catarrhal jaundice*)

Urobilinogen. Posthepatic bilirubin reaches the large intestine with the bile and there is transformed by the action of putrefactive organisms into urobilin Most of the urobilin is reabsorbed and carried back to the liver where the greater amount is stored, but some passes on to the kidney and is eliminated in the urine in the form of urobilinogen, a colorless precursor When liver function is depressed, the liver is less able to receive the urobilin, hence more of it is excreted by the kidney and is detectable as excess urobilinogen in the urine (Wallace and Diamond) In obstructive jaundice the bilirubin necessary for the formation of urobilinogen fails to reach the intestine and, therefore, urobilinogen is absent from the urine Since the significance of the test depends on the presence or absence of a free flow of bile into the intestinal canal, and as this may vary from day to day in certain pathological states, it may be necessary to examine the urine daily before any conclusion can be reached A strongly positive reaction is always indicative of parenchymatous damage to the liver A strongly positive reaction in a jaundiced person whose urine also contains bile, definitely signifies toxic hepatitis or other medical condition of the liver, though some cases of metastatic carcinoma of the liver have these findings A *daily negative* reaction in urine containing bile signifies a mechanical block in the common duct requiring surgical treatment In such a case the cause is usually carcinoma rather than a stone

Phosphatase and Jaundice Phosphatase is an enzyme which can hydrolyze phosphoric esters (such as glycero-phosphates and hexosephosphates) into inorganic phosphates There is a high concentration

TABLE XIV

Test	*Method*	*Normal Value*	*Extrahepatic Obstruction*	*Parenchymal Liver Disease*
Cephalin-cholesterol Flocculation	Hanger	Greater than 1+ at 24 hrs. is abnormal	1+ or below	Above 1+
Thymol Turbidity	Maclagen	0 to 4 units	0 to 4 units	Above 4 units
Serum Cholesterol (Total)	Schoenheimer and Sperry	180–220 mg/100 cc.	Above 225 mg/100 cc.	Below 225 mg/100 cc.
Serum Cholesterol (Esterified frac)	Schoenheimer and Sperry	50–65% of total	Above 50%	Below 50%
Alkaline Phosphatase	Bodansky	1 to 4 units per 100 cc.	Above 10 units	Below 10 units

formed by the blood of jaundiced human subjects Although tests demonstrated that no cysteine was present in normal plasma, definite reactions indicating cysteine were obtained on plasma from jaundiced animals The intensity of the test increased progressively with a tendency toward hemorrhage After the injection of brombenzene, a substance that combines with cysteine to form bromphenylmercapturic acid, which is excreted in the urine, the tendency toward bleeding was definitely reduced in the treated animals

Prothrombin In 1935 1937, Quick, who developed a satisfactory and simple method for the determination of the prothrombin content of the blood, and Dam and others, who discovered a hemorrhagic disease in chicks caused by a certain dietary deficiency, cast much light on the nature of the bleeding tendency in jaundice As a result of their work valuable therapeutic applications have been deduced As Quick (1938) pointed out there are four substances required for the clotting of blood (1) prothrombin, (2) thromboplastin, (3) calcium, and (4) fibrinogen Although it has been known that calcium and fibrinogen are not significantly altered in cholemic bleeding, no satisfactory methods for the determination of prothrombin or thromboplastin were available until Quick devised his test for prothrombin This test was based on the finding that the clotting time of oxalated plasma, when the amounts of thromboplastin and calcium are kept constant, is dependent on the concentration of prothrombin

The prothrombin concentration of human blood is very constant in

upon the relationship between the serum content of bilirubin and the phosphatase activity The test can serve this purpose only in the absence of other conditions capable of affecting phosphatase Roghman *et al* believe it is superior for this purpose to other available tests

Blood Cholesterol in Obstructive Jaundice and Liver Disease: In obstructive jaundice hypocholesterolemia is usually present The cholesterol esters rise concomitantly with the total cholesterol in about half the cases, but lag behind relatively in the remaining cases The cholesterol content of the blood roughly parallels the degree of obstruction and bilirubinemia In degenerative diseases of the liver, there is usually a pronounced divergence between the cholesterolemia and the bilirubinemia, the more severe the liver damage the greater the tendency of hypocholesterolemia, a drop in the cholesterol esters being even more accurately parallel to the severity of the damage In rapidly fatal cases in this group, the cholesterol esters are low or absent throughout the course of the disease In cholecystitis and cholelithiasis without biliary obstruction, the blood cholesterol is normal or insignificantly elevated

The urinary diastase concentration is pathologically increased in more than half of the patients with common duct stones although a normal urinary diastase is not evidence against choledocholithiasis In jaundice due to hepatitis, or malignancy of the head of the pancreas, the diastase concentration in the urine does not exceed the normal

Hoffbauer and his co-workers studied 77 cases of jaundice due to extrahepatic biliary obstruction and 70 cases due to parenchymal liver disease to estimate the value of liver function determinations performed on a single fasting blood serum sample In the following modified table the combination of tests found to be of most value are listed with normal and anticipated abnormal values They point out that the limitation of usefulness in these tests occurs in cases of parenchymal disease when cholangiolar functional impairment predominates, in which case the tests may be misleading (Table XIV)

The Bleeding Tendency in Jaundice Numerous analyses have shown that the total and "available" serum calcium of jaundiced subjects usually fall within normal limits Likewise, normal values have been found for blood platelets, plasma fibrinogen, fibrin, and even for the clotting time of the blood The blood clot, however, though forming as rapidly as normal, is large, friable and nonretractile

Carr and Foote observed that the addition of minute amounts of cysteine to normal blood shortened the coagulation time and changed the clot to a large, friable, nonretractile mass closely resembling that

with a diminution in blood prothrombin in chicks, and he suggested (July, 1937) that depletion of prothrombin in man is likewise the result of lack of vitamin K Since the new vitamin is fat soluble, he suggested that bile probably acts as a carrying agent for it across the intestinal tract and that in jaundice or biliary fistula, there is a lack of bile acids in the intestinal tract which causes faulty absorption of vitamin K A patient with a biliary abnormality often is on a low fat diet for a prolonged period of time This naturally limits his intake of fat soluble vitamins If a condition then supervenes which prevents the entrance of bile into the intestine, the absorption of vitamin K may cease almost completely and a serious deficiency in prothrombin may result

Vitamin K is normally present in the diet Since some is formed by intestinal bacteria as well, the daily feeding of bile to aid in its absorption prevents the fall of prothrombin incident to biliary fistula It also restores the prothrombin level to normal in cases in which it has already fallen The recovery in such cases is slow, however, unless the diet is enriched artificially with vitamin K The rate at which the prothrombin level rises with vitamin K therapy varies in different patients Usually a definite rise occurs within 24 hours, but treatment for three to eight days is generally needed to obtain the maximum response The failure of a satisfactory response to the administration of vitamin K indicates poor liver function and constitutes a useful liver function test

That prothrombin levels can be reduced by liver injury as well as by the deprivation of vitamin K has been emphasized by Stewart Smith *et al* have indicated experimentally that the liver is the site of the formation of prothrombin from vitamin K This work has been supported by experiments of both Bollman and others They found that severe hepatic injury is invariably associated with a deficiency in prothrombin in the circulating blood and that if the hepatic injury is severe enough, the administration of vitamin K is not effective in correcting this deficiency

Maintenance of normal blood prothrombin by oral therapy, as summarized by Butt, *et al* depends upon (1) a diet containing the antihemorrhagic vitamin K, (2) bile salts present in the intestine in adequate amounts, (3) a normal intestinal absorptive surface, and (4) normal liver function In many patients suffering from jaundice both the second and fourth factors are impaired To avoid the pitfalls of oral administration, parenteral vitamin K therapy, which obviates the necessity of the presence of bile salts, is preferable

In the management of jaundiced patients, therefore, it is of primary

normal persons It is at a normal level in hemophilia also and in the majority of jaundiced patients In a certain number of jaundiced patients, however, there is a definite reduction in prothrombin and a close relationship exists between prothrombin deficiency and the severity of the bleeding tendency There is a wide margin of safety, however, in the prothrombin factor, for the ordinary coagulation time of the blood may remain normal until the prothrombin has decreased by more than 80 per cent When it falls to below 20 per cent, however, the coagulation time begins to increase rapidly There usually is no serious bleeding until the prothrombin is reduced to very low levels, below 10 per cent The level at which bleeding actually occurs is very variable but in general patients with prothrombin levels below 50 per cent should be regarded as in the danger zone Many jaundiced patients show no tendency to hemorrhage before operation but have serious postoperative bleeding This is due to the fact that although there is a deficiency of prothrombin preoperatively it is not below the margin of safety With the trauma of operation, the prothrombin level is further lowered and falls into the hemorrhagic zone Scanlon *et al*, have suggested that this postoperative fall of prothrombin may be due to utilization of prothrombin for the formation of fibrinous exudate at the operative site The converse is also true A patient with very defective clotting due to low prothrombin is greatly benefited by even a small transfusion A transfusion restores only a fraction of the prothrombin but raises its concentration to a level at which normal clotting occurs This level may still be far below the normal prothrombin level Anderson *et al*, observed that during biliary tract surgery prothrombin activity becomes dangerously low from the fourth to the seventh postoperative day

That jaundice itself is not the direct cause of the deficiency of prothrombin is shown by the fact that only a small percentage of jaundiced patients show any hemorrhagic tendency, that often a very deeply jaundiced patient shows no abnormal hemorrhagic tendency and has no postoperative bleeding, and that patients with a biliary fistula and no jaundice at all, may have severe hemorrhage Moreover, Quick found normal prothrombin levels in all but a comparatively small number of jaundiced patients In cases with biliary fistulas, Howkins and Brinkhous found marked decreases in prothrombin

Vitamin K: The hemorrhagic disease discovered in chicks by Dam and others was found to be caused by the lack of a new accessory food substance which Dam named vitamin K (for "koagulations vitamin") Quick found that a lack of this substance in the diet was associated

vent bleeding is by transfusion plus vitamin K administration The prothrombin content of the blood should be the guide for the time and frequency of transfusion Stewart found that the response of the prothrombin level to treatment appears within 24 hours and lasts less than a week after vitamin K therapy is ended He believes, therefore, that daily administration of vitamin K is desirable

When transfusion is necessary because of bleeding due to lowering of the prothrombin level in the blood below 15 per cent, Rhoads and Panzer advise against the use of stored blood, since they have demonstrated that its prothrombin content diminishes rapidly on standing This rapid fall in the prothrombin level is partly due to temperature for blood stores at 37 degrees shows a rapid decline in prothrombin concentration Ziegler *et al* presented evidence that the prothrombin of decalcified blood decreases on standing, affording further evidence for the use of fresh blood only for the control of bleeding in jaundiced patients

In normal individuals there is apparently a continuous and relatively rapid formation and destruction of prothrombin, the latter occurring mainly, if not exclusively, in the liver Following hepatectomy, there is a rapid disappearance of prothrombin from the blood of animals Rhoads states that one factor is probably destruction in the lungs, for he found that the blood leaving the lungs regularly contains a lower concentration of prothrombin than does the blood in the pulmonary artery Clinically, however, hypoprothrombinemia is due largely to impaired formation, not excess destruction Some of the causative factors are dietary lack of vitamin K, nonabsorption of the vitamin and liver damage Such liver damage can best be counteracted by the administration of a diet high in protein and carbohydrates There are no known means for raising the prothrombin level above normal As pointed out by Dam and Glavind, the coagulation anomaly in cases of vitamin K depletion is due to a diminution of the ability of the blood to coagulate on the addition of tissue extract Mackie has stressed the fact, however that the coagulation time is not a measurement of the vitamin K status Even with a normal coagulation time, prothrombin deficiency may be so marked that bleeding may occur and the patient actually die from hemorrhage

Phthiocol Phthiocol, a naphthoquinone, which can be prepared synthetically, has been shown by Almquist and Klose to have physical and chemical properties similar to vitamin K and in common with a number of other naphthoquinones, to have antihemorrhagic activity in the bleeding tendency associated with hypoprothrombinemia Butt *et al*

importance to estimate whether there is impairment of hepatic function, using all available clinical data and one or more of the liver function tests If the test for synthesis of hippuric acid (Quick) is reduced much below 50 per cent, the patient is apt to be a poor surgical risk If the prothrombin level is low and cannot be brought to near normal by the administration of vitamin K, poor liver function is further confirmed In such instances, unless immediate operation is extremely urgent, patients should be given preoperative treatment to improve liver function, namely, a diet high in proteins and dextrose with added calcium and vitamin D

Postoperative hypoprothrombinemia sometimes occurs in patients with obstructive jaundice or biliary fistula despite some preoperative vitamin K and bile salt therapy Allen and Livingstone found that this is not due to any type of anesthesia or to loss of blood They concluded that it results from failure to replenish the body's reserve store of vitamin K or prothrombin preoperatively, that is, it is due to inadequate preoperative therapy

Allen and Vermeulen have presented evidence to indicate that prothrombin is rapidly destroyed in man Blood prothrombin determination, therefore, does not indicate the state of the body reserves of vitamin K Even though the preoperative level of prothrombin may be normal and body stores of the vitamin may be virtually depleted Allen and Vermeulen advise that vitamin K and bile salt therapy be given preoperatively in all cases of jaundice or biliary fistula Vitamin K is found abundantly in cabbage, spinach, alfalfa, and fish meal It may also be produced by bacterial activity in the intestinal tract, a fact of some importance, since aureomycin and chloromycetin which are used to sterilize the intestinal tract preoperatively, may so lower bacterial activity in the intestine that insufficient vitamin K is produced Bleeding occasionally occurs in such cases due to the consequent lowering of the prothrombin level Prothrombin deficiency can be treated by the administration of vitamin K (powdered alfalfa leaf or extract) and bile, or preferably bile acids to assist in its absorption It is more commonly given parenterally since by this route bile salts are not needed for its absorption Dramatic relief from the bleeding tendency is obtained in most cases by this therapy Response to orally administered vitamin K and bile salts is not entirely uniform, probably due to unequal functional capacity of the liver in different patients In postoperative biliary fistula, therapy should be continued as long as the fistula remains open If the prothrombin concentration in the blood falls below 15 per cent, the only promptly effective treatment to pre-

terial which has been purified till free of this vitamin still retains its antianemic potence

The question arises as to the relation of the extrinsic (beefsteak) factor and the intrinsic factor to antianemic liver material and anti anemic stomach material Since desiccated whole stomach is potent by itself, it contains both extrinsic factor (possibly in the muscle elements) and intrinsic factor (secreted by the mucosa), the interaction of the two generating antipernicious anemia factor The latter is then stored in the liver (and also to some extent in the kidney), giving these their antianemic potency Addison's anemia is due to lack of the intrinsic factor, extrinsic factor being adequately supplied in the normal diet

Spies and other workers have been able to produce hemopoietic responses in persons with macrocytic anemias by the use of new synthetic compounds, folic acid (pteroyl glutamic acid) and thymine (5 methyl uracil) Neither substance is a complete treatment for pernicious anemia

More recently Rickes *et al* have isolated vitamin B_{12} from liver Spies and his co workers believe this substance to be the most effective antianemic factor known In addition to production of an effective hematologic response, it protects patients from the accompanying neurological complications of this disease

THE RETICULO ENDOTHELIAL SYSTEM

The functions of the reticulo-endothelial system are

1. Destruction of red cells and transformation of their hemoglobin into bilirubin
2. Defense of the body against toxins and infections by antibody formation and phagocytosis
3. Storage of certain lipoid substances
4. Regulation of the metabolism of iron

The reticulo-endothelial system is composed of certain cells of the spleen, bone marrow and lymph nodes and the Kupffer cells of the liver In man and in mammals generally the spleen and bone marrow contain the bulk of the reticulo-endothelial system Reticulo-endothelial cells are identified by their property of retaining certain dyes when these are injected intravenously in vivo The simple endothelium which lines the blood vessels does not possess this property and is not a part of the system That fibrinogen is produced by the reticulo-endothelial system is suggested by Held and Behr from their experiments and by reasoning from the fact that the system is known to be the site of formation of certain blood antibodies protein in nature

administered synthetic phthiocol intravenously in 10 patients with increased prothrombin times, in each instance the prothrombin time was reduced to nearer the normal level and no untoward reactions occurred Allen and Julian have obtained good results in similar cases from the use of another synthetic substance, 2-methyl-1 1, 4-naphthoquinone, resembling vitamin K This finding was confirmed by Norcross and McFarland who determined the minimum effective dose for adults to be 2 milligrams The use of bile salts is not necessary in order to obtain the response, but the presence of severe liver damage reduces the response

It is generally felt that the determinations of prothrombin time or better the level of prothrombin by the plasma dilution method is the safest means of measuring the bleeding tendency in jaundice and of determining the effect of vitamin K therapy In accord with this impression were the findings of Cheney He recommended an average therapeutic dose of 2 to 4 milligrams of vitamin K daily for two days before and seven days after operation and advised that therapy be continued indefinitely in cases in which the cause of the deficiency cannot be relieved Since no toxic symptoms have been demonstrated following the administration of vitamin K most physicians recommend the use of much larger doses from 10 to 60 milligrams daily preoperatively and 10 to 20 milligrams daily postoperatively in jaundiced patients

ANTIANEMIC PROPERTY OF THE LIVER

Castle showed that certain foodstuffs (e g , beefsteak) having no antianemic properties became actively antianemic when acted upon by gastric juice This factor in foodstuffs was called the extrinsic factor and that in gastric juice the intrinsic factor The lack of either of these substances causes the Addisonian type of anemia The intrinsic (gastric) factor is presumably an enzyme, it is completely inactivated by heating to 70°C Gastric acidity is not inseparably related to the intrinsic factor for acid gastric juice from a patient with tropical sprue, when mixed with meat and fed to a patient with pernicious anemia fails to induce a reticulocyte response and, therefore, does not contain the intrinsic factor Conversely, in many elderly individuals achlorhydria without anemia occurs The nonacid gastric juice from such an individual when tested in a case of pernicious anemia is found to contain the intrinsic factor The extrinsic factor, which is in beefsteak and is found also in large amounts of yeast, is not identical with or closely allied to vitamin B_2 (G) as was formerly thought Liver ma-

terial which has been purified till free of this vitamin still retains its antianemic potence

The question arises as to the relation of the extrinsic (beefsteak) factor and the intrinsic factor to antianemic liver material and anti anemic stomach material Since desiccated whole stomach is potent by itself, it contains both extrinsic factor (possibly in the muscle elements) and intrinsic factor (secreted by the mucosa), the interaction of the two generating antipernicious anemia factor The latter is then stored in the liver (and also to some extent in the kidney), giving these their antianemic potency Addison's anemia is due to lack of the intrinsic factor, extrinsic factor being adequately supplied in the normal diet

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THE SPLEEN

Functions of the Spleen The functions of the spleen are as follows

1 Destruction of red blood cells and possibly platelets, and formation of bilirubin from the hemoglobin liberated Normally the spleen is the chief organ for performing this function, though the bone marrow and liver take part in it to some extent After splenectomy the other reticulo-endothelial organs, namely the liver, bone marrow and lymph nodes take over the function completely After removal of the spleen there is a prompt decrease in the amount of urobilin excreted in the urine, since normally liberated hemoglobin is transformed into bilirubin, the necessary precursor of urobilin, chiefly by the spleen

2 Maintenance of a reserve supply of red cells The splenic venules are lined by large spindle-shaped cells which are loosely arranged so that the walls are incomplete, red cells pass out into the reticulum and among the phagocytic cells of the pulp The organ is much larger during life than after death, in the cat it is four times as large during life Though the smooth muscle of the capsule of the spleen undergoes contractions regularly several times a minute, ordinarily there is not much interchange of blood cells between the spleen and the circulation, this is evidenced by the fact that inhaled carbon monoxide penetrates into and is released from the spleen very slowly The adequate stimulus for strong contraction of the spleen and pouring of the reserve cells into the circulation is oxygen lack from any cause The lack of oxygen does not affect the spleen directly, it in some way excites the sympathetic nerve fibers which supply the spleen (splanchnic nerve) Also adrenalin secreted in response to anoxemia probably augments the contraction of the spleen Splenectomized animals die more quickly from hemorrhage or carbon monoxide poisoning than normal animals, due to loss of this reservoir function of the spleen

3 Formation of red cells and lymphocytes, normally a function of the spleen in the fetus and child, may be resumed in adult life in case of need

4 Regulation of iron metabolism and storage of iron Storage of iron is impaired after splenectomy and there is excessive excretion of iron by the kidneys

5 Storage of certain lipoids in the reticulum cells, more marked when blood cholesterol is elevated

6 Protection against toxins, bacteria, parasites, etc , by antibody formation, phagocytosis and other defensive reactions Splenectomized animals cannot be actively immunized against tetanus toxin, also they succumb more readily to infections of all sorts than do normal animals

7 Regulation of blood volume The role of the spleen as a regulator of the circulation is discussed by Holman with special reference to the temporary elevation of blood pressure which occurs following splenectomy He points out that since the walls of the finer veins in the spleen are incomplete the circulation in the organ is an "open" one The spleen is like a modified blood vessel, being capable of constriction and relaxation Its blood is twice as rich in red cells as blood elsewhere, and 50 per cent richer in hemoglobin The circulating blood volume of the body can be augmented from the spleen by as much as 20 per cent, this function is made evident by the reduced size of the organ following hemorrhage and during exercise, and its range is increased when the spleen is pathologically larger than normal In splenomegaly, an increase in total blood volume occurs to compensate for the increased capacity of the spleen, this is the cause of the postoperative rise of blood pressure after splenectomy This rise is analogous to that which occurs after excision of a large arteriovenous fistula, the enlarged spleen is comparable to a large varicose aneurysm, in that each causes an increase in total blood volume to develop, and excision diminishes the capacity of the vascular system Holman found that the systolic pressure rose 20 to 25 mm Hg and remained elevated for a few days In all cases the artery was tied first and the spleen shrank visibly before the vein was tied

The Effects of Extirpation of the Spleen are as follows

1 Mild or moderate anemia, becoming marked after about six weeks and followed by gradual recovery over a period of a few months In man many immature and nucleated red cells appear in the blood The ability to withstand hemorrhage and exertion is diminished to a greater degree than would correspond to the severity of the anemia, indicating a decreased reserve oxygen-carrying capacity

2 Decreased fragility of the red cells (increased resistance to hemolysis)

3 Leucocytosis, mainly polynuclear, of 20,000 to 40,000 within 24 hours, followed by slow return of the white cell count to normal over a period of months Increased number of eosinophiles

4 Temporary increase in the number of platelets The mechanism by which these blood changes are brought about is not understood

5 Hypertrophy of lymph nodes and hemolymph nodes

6 Bone marrow hyperemia and hyperplasia, sometimes causing pressure absorption of bone and resulting in gnawing pain in the long bones

7. Hyperplasia of the thymus
8. Increased iron elimination
9. Vomiting of blood sometimes occurs immediately after operation

Postoperative fatal thrombosis of the splenic and portal veins sometimes occurs following splenectomy Bryce states that it is more likely to occur in patients with a normal or nearly normal platelet count, while there is less danger of thrombosis if the platelet count is low

Indications for Splenectomy Splenectomy is advisable in the following conditions

1 Hemolytic ("acholuric") jaundice, in which the red cells are abnormally fragile for some unknown reason and are destroyed excessively by the spleen Splenectomy cures the condition

2 Banti's disease of adults, which is apparently identical with "splenic anemia" in children Possibly the basic factor is a chronic infection of unknown type localized in the spleen Sclerotic changes in the splenic vein are often present, sometimes causing gastric hemorrhages and making removal difficult

A favorite theory of the etiology of Banti's disease has been that of a primary splenomegaly and a subsequent hepatic cirrhosis, due to a hypothetical toxic agent This theory is rejected by Rousselot, who maintains that the splenomegaly can be entirely explained on a mechanical basis, that is, as the result of a primary obstruction somewhere in the extrahepatic portal system with an associated portal hypertension In all the cases (four) in which he tested the portal venous pressure, he found portal hypertension present He calls attention to the frequency of anomalies of the portal system In his opinion the prognosis and the variations in the clinical behavior in cases of Banti's disease depend on (1) the site of the obstructive lesion, and (2) variations in the anatomy of the venous pattern

3 Purpura hemorrhagica, in which the platelets are decreased, the bleeding time prolonged (10 to 20 minutes instead of the normal two to four minutes), and the permeability of the capillaries to blood abnormally increased (probably the primary factor) The coagulation time is normal Splenectomy often causes cessation of hemorrhages, probably because of increase in platelets compensating for the defective capillaries However, the relief often lasts long after the increase in platelets has disappeared, so that the matter is still obscure

In a case of Felty's syndrome, a rare condition characterized by chronic arthritis, splenomegaly and leukopenia, marked benefit from splenectomy has been reported by Hanrahan and Miller

In cirrhosis of the liver with bleeding varices of the esophagus and

stomach, splenectomy has been recommended by some authors Mandel and Marcus point out that when the flow of portal blood through the liver is impeded by cirrhosis, the splenic blood passes through the collateral channels which constitute the varices By splenectomy, therefore, a considerable portion of the blood which burdens the varices is eliminated, and the danger of hemorrhage is diminished

RETICULO-ENDOTHELIAL CELLULAR DEFENSE

Study of the cellular content of blisters produced in the skin by cantharides is recommended by Ebhardt as a valuable method of estimating the body's cellular defense mechanism He regards blister formation as a mobilization of the reticulo-endothelial cells of the skin He found that in acute appendicitis and its complications there was a predominance of pus cells in the progressing stage of the disease and a gradual shift to lymphocytic cells in the blister fluid in the course of encapsulation and absorption of pus within the abdomen This sequence, leucocytic combative phase followed by lymphocytic convalescent phase in the cantharides blister, was observed after operation or injury in a normal individual, trauma acting as a non specific irritant Ebhardt believes that the occasional remarkable benefit from an exploratory operation in tuberculous peritonitis may be ascribed to such stimulation of the reticulo-endothelial system

Vincent M Iovine M D

Chapter XII

VITAMINS IN SURGERY

GENERAL nutrition, resistance to infection, prevention of hemorrhage, and wound healing are influenced by the various vitamins It is essential, therefore, to maintain an adequate vitamin intake during the preoperative and postoperative periods

The dietary habits of the patient will often give a clue concerning vitamin deficiencies and the nature of the existing disease upon the utilization of food should also be considered For example, in cases of intestinal obstruction, malignant or inflammatory lesions of the digestive tract, the possibility of the effects of the assimilation and utilization of vitamins will become important Obstructions of the common bile duct or exclusion of bile from the intestines for any other reason may effect fat metabolism and alter the absorption of the fat soluble vitamins, carotene and vitamins B and K The reserve supply of vitamins may be depleted from the effects of chronic disease

Means of detecting subclinical degrees of vitamin deficiencies have been developed and these laboratory tests should be employed if deficiencies are suspected

In extremely ill patients confined to a liquid diet, additional vitamins should be supplied in the form of milk, cream, ground liver, whole grain cereals and fruit juices If necessary, this supplemental diet should be supplied by catheter feedings

VITAMIN A

Vitamin A is formed from ingested carotene, probably in the liver, where large amounts of it may be stored About 95 per cent of all the vitamin A in the body is held in the liver and the reserves so stored can be built up so as to supply the body's needs for a long period of time The average daily requirement for man is not accurately known Since it is stored in the liver and also is fat-soluble, large amounts of vitamin A are present in animal and fish livers and in fish liver oils Other rich sources are green, leafy vegetables, green peas and beans, yellow vegetables containing carotene, milk and eggs

Bile is essential for the absorption of carotene and any condition which excludes bile from the intestine prevents the absorption of carotene, but apparently does not interfere with the absorption of vitamin

A itself Ingested liquid petrolatum likewise markedly diminishes the absorption of carotene, but not that of vitamin A Disturbances of fat metabolism as in obstructive jaundice, pancreatic disease and prolonged diarrhea may cause a deficiency of vitamin A

The most conspicuous ill effects of vitamin A deficiency are changes in epithelial tissues in general—chiefly, epithelial atrophy and desquamation followed by keratinization This metaplasia occurring in the respiratory mucosae has been suggested as a factor predisposing to postoperative pulmonary infections, but there is no conclusive evidence establishing this relationship of vitamin A deficiency to such infections Some investigators believe that vitamin A deficiency is a factor in the production of urinary calculi, but many other authorities fail to find any such relationship Holman cites evidence that vitamin A deficiency may possibly predispose to the development of suppurative parotitis

It was observed by Brown and Brown, that solitary urinary bladder stones were common in boys in Syria These authors obtained evidence that these stones form around keratinized epithelium of the urinary tract, and that this keratinization is the result of seasonal vitamin A privation

Thyroxin has the property of preventing or relieving the symptoms of excessive dosage of vitamin A, and conversely vitamin A can diminish the effects of thyroxin in the body Patients with hyperthyroidism usually have abnormally low amounts of vitamin A in their blood, and it is established that vitamin A is more rapidly destroyed when the metabolic rate is high Though some patients with hyperthyroidism have been reported to have improved as the result of a high intake of vitamin A, the therapeutic value of this vitamin in hyperthyroidism is not generally accepted

Though a general anti infective property has been attributed to vitamin A by some authors there is no conclusive evidence of such a property If there exists any increased susceptibility to infection in the presence of vitamin A deficiency, it could as well be explained on some other basis, such as a coincident poor state of general nutrition

Fish oils rich in vitamin A have been reported to inhibit infection and stimulate healing of wounds, burns and ulcers when applied locally to such lesions Puestow *et al* in controlled experiments on pigs receiving a diet not deficient in any vitamin, noted a definite shortening of the healing time of burns which were treated with ointments containing vitamins A and D regardless of which of these vitamins predominated Any value of vitamin A in lessening infection and stimulating healing in surgically produced wounds has not been established conclusively

VITAMIN B

The vitamin B complex includes a large number of factors Important of these are vitamin B_1, or thiamin, which prevents beriberi, nicotinic acid, which prevents pellagra, riboflavin, folic acid and vitamin B_{12}, both very important in the therapy of pernicious anemia

The richest sources of vitamin B are yeast, wheat germ, whole cereals, meats and dairy products

The intake of vitamin B may be rendered inadequate by gastrointestinal disorders such as pyloric obstruction and colitis which interfere with the intake or absorption of adequate amounts of vitamin-containing foods Utilization of the vitamin may be accelerated beyond the rate of intake by infection, fever and physical activity

Thiamin (Vitamin B_1) : The neurological manifestations of vitamin B_1 deficiency are bilateral and symmetrical polyneuritis, involving first and predominately the lower extremities Peripheral neuritis having a different distribution than this is probably not due to vitamin B_1 deficiency alone The circulatory manifestations of vitamin B_1 deficiency are edema, serous effusion, congestive heart failure and sudden circulatory collapse, they are more likely to occur in subjects with only mild neuritis because these subjects are capable of greater muscular exertion than those having advanced neuritis

Vitamin B_1 deficiency should be particularly suspected in the indigent and low income group, in persons who have faulty dietary habits and food idiosyncrasies, in alcohol addicts and in patients who have diseases which alter the vitamin B_1 requirements The principal factors which raise the vitamin B_1 factors are increased total metabolism, reduced absorption due to disorder of the gastrointestinal tract and increased excretion of the vitamin (e g , due to polyuria)

For prevention of vitamin B_1 deficiency, the ratio vitamin B_1 total calories must be above a certain level, 0 5 milligram of thiamin chloride for each 1000 calories provides a sufficient margin of safety for persons in normal health In disease, however, the factors mentioned above, which alter the vitamin B_1 requirement must be considered In diseases which cause interference with absorption the parenteral route should be used As Jolliffe states, there is danger of inducing vitamin B_1 deficiency in patients maintained with parenteral feedings of dextrose, for example, postoperative patients This can be prevented by the daily administration of 5 to 10 milligrams of thiamin chloride in such cases

The tachycardia in hyperthyroidism may be partly due to B_1 deficiency according to Frazier and Ravdin, who found that preoperative

administration of large amounts of vitamin B_1 was followed by a greater than usual fall in the heart rate and also by more rapid clinical improvement as to appetite and body weight.

Ochsner and Smith report relief of pain of varicose ulcers of the legs following administration of large doses of vitamin B_1 by mouth

Nicotinic Acid Nicotinic acid and related compounds relieve many of the symptoms of pellagra Pellagra affects chiefly the alimentary tract, skin and nervous system One of its earliest symptoms is a particular type of glossitis characterized by swelling and reddening of the margins and tip of the tongue, extending to involve the entire tongue as the disease progresses Prodromal nervous symptoms are hyperesthesia to all forms of sensation, fatigability and anxiety with a tendency toward mental depression.

Riboflavin Riboflavin deficiency is characterized by lesions at the corners of the mouth (cheilosis), ocular and cutaneous symptoms, and decrease of vigor and of the sense of well being

The vitamin B complex may be administered in the form of multiple vitamin capsules Vitamin B_1, however, is given as thiamin chloride, 50 to 200 milligrams daily, either intramuscularly or by mouth The intramuscular route is preferable in cases in which poor absorption has been demonstrated After saturation, which may be recognized by the detection of a distinct odor resembling burnt rubber in the urine, the dose may be reduced to 10 milligrams daily Nicotinic acid is given for the treatment of pellagra in doses of 500 milligrams per day by mouth, or 50 to 80 milligrams parenterally Riboflavin is given in doses of 3 to 5 milligrams per day

VITAMIN C

Vitamin C (ascorbic acid) which prevents scurvy, can be synthesized (in the body) by all animals except man, the monkey and the guinea pig The daily requirement of vitamin C for man is from 29 to 100 milligrams, it varies greatly under different physiological and pathological conditions Vitamin C is present in varying concentrations throughout the body The blood contains normally 0 7 to 1 4 milligrams per 100 cubic centimeters The richest food sources of vitamin C are the citrus fruits and the green leafy vegetables

The basic physiological role of vitamin C is the promotion of normal production and maintenance of the intercellular connecting or cement substances of the supporting tissues of the body, particularly collagen The fundamental pathological change resulting from an inadequate

amount of this vitamin is a defect in this intercellular substance The latter may develop faultily or it may undergo liquefaction and absorption, in any case it is weakened in its main function, mechanical support of tissues

Hemorrhagic Diathesis The hemorrhagic tendency in severe vitamin C deficiency, manifested first by capillary fragility is attributed to weakening of the intercellular structures of the blood vessel walls

Patients with bleeding duodenal ulcers have been found to be markedly deficient in vitamin C In most patients with peptic ulcer the vitamin C level in the blood is low, regardless of diet This deficiency is believed to be secondary to the ulcer, rather than a predisposing cause of the ulcer Wound healing is promoted by vitamin C, a deficiency impairs the production and maintenance of the intercellular substance related to the growth of fibroblasts, and may perhaps be an important causative factor in the disruption of wounds

Dietary deficiency of vitamin C is very common It is sometimes the result of a therapeutic diet, in peptic ulcer for example Interference with the ingestion or absorption of vitamin C may occur in certain diseases or disturbances, as in obstructing lesions of the gastrointestinal tract and conditions causing vomiting or diarrhea

An increased demand for and utilization of vitamin C are characteristic of hyperthyroidism, peptic ulcer, malignancy and infections Though subclinical scurvy is so common in infections that it has been considered a predisposing cause, most observers believe the vitamin C deficiency to be the result of the infection The best test for vitamin C deficiency is the determination of the vitamin C concentration in the blood plasma by titration The test is accurate, rapid and fairly simple

Wound Healing · In two-thirds of 188 surgical patients Bartlett *et al* found the fasting level of vitamin C to be less than 0 5 milligram per 100 cubic centimeters This deficiency was not limited to any one pathological condition There was a drop in the fasting plasma vitamin C level following operation in all cases, with gradual return to the preoperative value During the immediate postoperative period administered vitamin C disappeared from the blood more rapidly than normally The authors suggest that this may be due to an increased need for the vitamin for tissue repair and wound healing

Holman found that of 70 surgical patients from low economic groups, 44 per cent were deficient in vitamin C, having from 0 15 to 0 30 milligram of vitamin C per 100 cubic centimeters of blood

Preclinical scurvy has been found to be very frequent in surgical patients suffering from lesions producing intestinal obstruction, malignancies and other debilitating diseases Wound disruption is particularly common in these groups of patients In all patients in whom vitamin C deficiency exists preoperatively, the vitamin should be administered for a week or longer before operation to permit saturation of the tissues The vitamin may be given by mouth in the form of fruit juices or as ascorbic acid tablets, it may be given intramuscularly, or the sodium salt of ascorbic acid may be given intravenously

Following operation on patients having a decreased vitamin C concentration in the plasma there occurs an immediate and marked drop of plasma vitamin C to still lower levels, as stated above, yet the patients do not show clinical signs of scurvy even if the plasma level of vitamin C reaches zero

Lund and Crandon produced scurvy experimentally in a man by means of a vitamin C free diet maintained for six months The ascorbic acid level fell to zero in the blood plasma in 42 days and in the white blood cells in 122 days A wound made three months after the beginning of the diet failed to heal These authors find that plasma vitamin C determinations alone are not sufficient evidence on which to base treatment of surgical patients, as the great majority of patients with low levels are in no manifest danger due to the deficiency They recommend, however, that if there is a history of long continued, marked deficiency of intake of vitamin C, the patient being prepared for operation be given treatment (1 to 4 grams of ascorbic acid daily)

VITAMIN D

The basic effect of vitamin D in the body is to promote the normal metabolism of calcium and phosphorus It increases the absorption and utilization of these elements and diminishes their intestinal excretion Most of the commonly used foods contain little or no vitamin D The richest natural source of vitamin D is fish liver oils The vitamin is also present in eggs, milk, fats and some meats The normal daily requirement for adults has not been determined

The chief surgical importance of vitamin D has to do with parathyroid tetany In the treatment of this condition, vitamin D is beneficial ordinarily it must be used in conjunction with the administration of calcium and of parathyroid extract Possibly vitamin D is also a factor promoting the healing of fractures and of soft tissue wounds, although these properties have not been conclusively demonstrated for patients who are not deficient in vitamin C

VITAMIN K

This vitamin is discussed in connection with the bleeding tendency in jaundice

VITAMIN P

Zacho was able to produce capillary weakness in animals fed on a flavone free diet Vitamin P is derived from flavone dyes found naturally in yellow plant pigments According to Levitan, the term, vitamin P, exceeds old limits one usually associates with the word vitamin

Capillary resistance may be measured by tourniquet, by graded suction, or by positive pressure tests It varies with age and nutritional status and also (except in the newborn) in various parts of the body During the first few weeks of life capillary resistance is about 500 millimeters of mercury It gradually diminishes to about 150 millimeters of mercury in the adult

Kugelmass found that citrin did not alter the concentration of any of the blood components concerned in clotting fibrinogen, prothrombin or platelets, but that, given orally, it was beneficial in the treatment of children with certain types of purpura

Rutin is another type of vitamin P, although not as potent as esculin Rutin has been employed clinically to reduce the incidence of cerebral hemorrhage in hypertension and Shanno reported some success in controlling "idiopathic" hemoptysis Most recently Levitan suggests that vitamin P has a stabilizing effect on the ground substance found in the erythrocyte membrane and the arterial wall

Some authorities believe the term vitamin P should be discontinued since it is not a single substance and its role in nutrition poorly understood

METABOLISM

General metabolism deals with the balance between the intake and output of energy and of food materials by the body Special metabolism deals with the successive chemical changes which the various food materials undergo between ingestion and excretion

Energy of Metabolism The most direct way to determine the rate of metabolism is actually to measure the heat produced by the body by means of a calorimeter chamber in which the patient remains for a given period of time But this method is difficult and expensive In general, the amount of heat produced is directly proportional to the rate of combustion (oxidation) of the foodstuffs and hence to the amount of oxygen consumed, therefore, measurement of the oxygen consumed

during a given period is a satisfactory and much simpler method of determining the metabolic rate

Metabolic Rate The same amount of oxygen consumed can, of course, represent different amounts of heat, according to the type of fuel burned, but this difference is not very great with reference to the three types of substances which are the only sources of energy in the body, namely fats, proteins and carbohydrates A gram of fat, though it yields much more heat than a gram of protein, requires much more oxygen for its combustion Therefore, for each cubic centimeter of oxygen used in the oxidation of the two substances, though there is some difference in the amount of heat produced, the difference is not great.

Measurement of oxygen consumption alone can, therefore, give a fairly satisfactory indication of the metabolic rate even though the type of food being burned at the time is not known The latter source of error is practically eliminated, however, by always performing the metabolism test (i e , the measurement of oxygen intake per unit of time) under standard fasting conditions, for the relative amounts of the three types of fuel substances oxidized under such conditions are known

The types of fuel being burned could actually be determined, if that were necessary, in the following manner The amount of protein burned in a given period of time is readily calculated from the amount of nitrogen excreted during that time, for nitrogen constitutes of about 16 per cent of protein The relative amounts of fat and carbohydrate being burned are deduced from the amount of CO_2 excreted in proportion to the amount of oxygen consumed This deduction is possible because of the fact that carbohydrates contain relatively more oxygen and less carbon than fats by reason of their chemical formula e g , $C_6H_{12}O_6$ glucose versus $C_{18}H_{34}O_2$ oleic acid, the carbon oxygen ratio being 1 1 and 9 1, respectively Therefore when a certain amount of oxygen is consumed in the oxidation of carbohydrates, more CO_2 is formed than when the same amount of oxygen is used in the oxidation of fat.

The ratio (by volume) between the amount of CO_2 produced and of oxygen consumed in the process of combustion is known as the respiratory quotient of the substance burned Its value is 1 0 for carbohydrates and 0 7 for fats When a mixture of carbohydrates and fats is oxidized the respiratory quotient necessarily lies between 1 0 and 0 7, and it approaches one or the other value according to which substance is present in greater amount

The respiratory quotient of protein is 0 82, but this fact is not used in estimating the amount of protein oxidized because this knowledge can be gained readily by measurement of the nitrogen excretion, as mentioned previously

The only factors which alter the respiratory quotient of the body during rest are diet and disease, especially disturbances of acid base balance In the normal resting and fasting adult the amount of energy produced continuously as a result of the metabolic processes of the body is about one calorie per kilogram of body weight per hour, or 70 calories per hour for an individual of average size This is equivalent to 1680 calories per day For some reason this "basal" heat production increases when food is taken, even though the subject still remains at rest This increase in metabolism resulting from the taking of food is called the specific dynamic action of food It varies in magnitude for the different types of food, being greatest for protein, which causes an increase of about 30 per cent of the basal metabolism

The usual mixed diet causes the fasting heat production to increase by about 10 per cent, or about 168 calories per day in the average sized person The basal metabolism (1680 calories) plus this increment due to food (168 calories) represents the number of calories required daily (1848 calories) for maintenance of an average normal adult at rest in bed This figure varies somewhat with age and is somewhat higher in males than in females It is different, too, in persons of the same weight but different height and body configuration Investigation has shown that this variation in metabolic rate with shape of body is related to the surface area of the body, that is, the number of calories produced per unit of surface area is constant, not per unit of weight

Muscular activity, of course, increases the rate of metabolism but does not increase basal metabolism, because when there is muscular activity, metabolism is no longer "basal " Practically the only abnormal conditions which increase the basal metabolism are fever, thyroid disease and leukemia The reason for the increased basal metabolic rate in leukemia is unknown

MATERIALS OF METABOLISM

Carbohydrates perform the following functions in the body 1 They constitute a readily available source of energy 2 They play a role in the combustion of fat 3 They take part in the contraction of all types of muscle The whole blood stream contains a total of only about 5 grams of sugar

Fats and lipoids have the following uses in the body 1 They are

essential constituents of all cells 2 They supply large amounts of energy and serve to store energy 3 They are related in some way to vitamins A and D absorption

Protein has the following uses in the body 1 It is essential to tissue repair, for which it is the sole source of available nitrogen and sulfur 2 It supplies the special amino acids required for the formation of various hormones and enzymes 3 It supplies energy and also stimulates metabolism Protein digestion occurs chiefly in the small intestine, partly in the lumen and partly in its wall One hundred grams of protein is usually recommended as the normal daily ration This amount allows for an adequate margin of safety

The amino acids which are not used as such for the construction of tissue proteins are broken down in the liver When a considerable portion of the liver is severely damaged, the conversion of ammonia to urea is impaired with the result that the urine contains relatively more ammonia and less urea This occurs only in rather grave conditions, such as acute yellow atrophy and phosphorus poisoning, but occasionally such alteration of the ammonia urea ratio in the urine may be of aid in diagnosis

Acidosis in Starvation Starvation leads to acidosis because lack of carbohydrates results in incomplete combusion of body fats with formation of B-oxybutyric acid, etc Administration of carbohydrate or fat checks this steady body protein combustion, carbohydrate, since it is the "quickly available fuel," is a "better protein sparer" than fat

The Committee on Food and Nutrition of the National Research Council recommends the following daily dietary allowances of specific nutrient factors for a moderately active adult male Calories, 3000, Protein, 70 grams, Calcium, 0 8 gram, Iron 12 grams, vitamin A, 5000 international units Thiamin (B_1), 1 8 milligrams, Nicotinic acid, 18 milligrams, Riboflavin, 2 7 milligrams, Ascorbic acid (C), 75 milligrams vitamin D, 400 to 800 international units

Vincent M Iovine

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Chapter XIII

GENERAL PHYSIOLOGY OF THE BODY FLUIDS

THE MECHANISM OF FLUID INTERCHANGE BETWEEN BLOOD AND TISSUES

FLUID interchanges between the blood and tissue spaces are regulated by the capillary blood pressure, which constantly tends to drive fluid through the capillary wall, and the osmotic pressure of the plasma colloids, which draws fluid back from the tissue spaces into the blood stream The normal differential in pressures within the capillary loop is produced by these different pressures a constant osmotic 30 millimeter of mercury hydrostatic pressure of the blood, and an 8 millimeter of mercury hydrostatic pressure in the tissue fluids, thus producing an effective hydrostatic pressure of 22 millimeters of mercury within the vascular component. There exists a 25 millimeter of mercury osmotic pressure in the blood as compared to a 10 millimeter of mercury osmotic pressure within the tissues, thus giving an effective osmotic pressure of 15 millimeters of mercury in the vascular division of the bed This ultimately ends in a driving force in the vessels equal to 7 millimeters of mercury

Water, crystalloids, and a small amount of protein leave the vessels for the tissue spaces on the arterial side of the loop, whereas water, crystalloids nonprotein nitrogenous components and infinitesimal quantities of proteins are withdrawn from the tissues on the venous side The lymphatic system is situated between the capillary loop and the extracellular spaces and absorbs water, proteins and particulate material The flow and quantity of lymph is, therefore dependent upon and related to the physiological exchange in the capillary bed Also, the interstitial fluid is continually produced and renewed from the blood serum (Figure 23)

The volume of interstitial fluid is calculated to be 35 000 cubic centimeters, or represents 15 per cent of the body weight. It has the same chemical composition as plasma but the latter has a higher protein content

Variations in the relationships of the various substances producing the differential in pressures in the capillary loop effects the pattern of

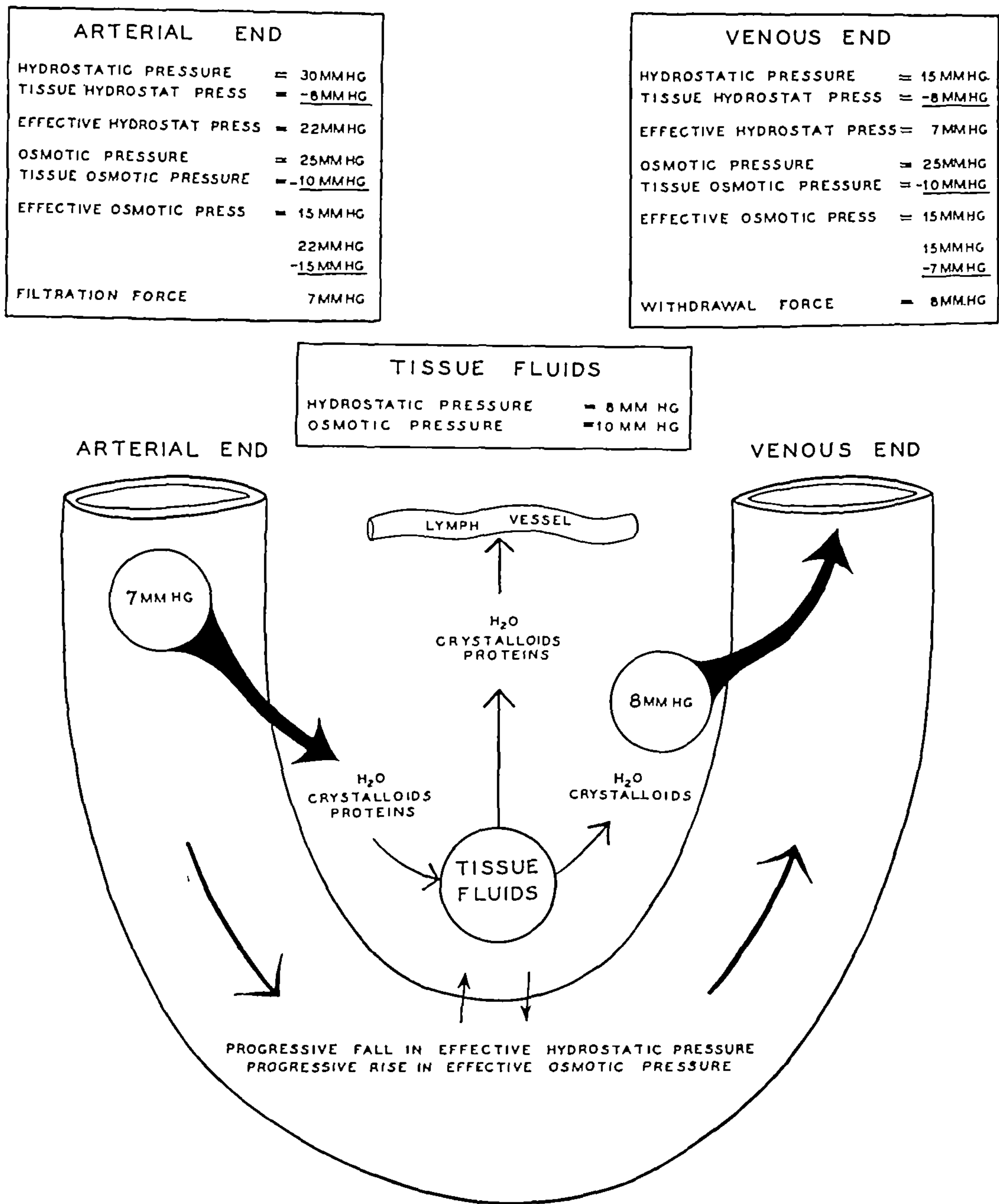


FIG 23 PHYSIOLOGY AND FLUID EXCHANGE IN THE CAPILLARY BED
The filtration force of 7 mm of Hg represents the positive difference of the hydrostatic and osmotic pressures on the arterial side of the capillary loop in favor of the intracapillary hydrostatic pressure, whereas the 8 mm Hg of withdrawal force indicates the greater intervascular osmotic pressure In the central portion of the capillary loop, there is a balance of pressures that produces a to and fro exchange (White, C S and Weinstein, J J *Blood Derivatives and Substitutes*, page 27)

exchange Thus, in venous obstruction, the pressure in the capillaries rises, always *remaining* above that in the veins, the increment of capil lary pressure being proportional to the increase of venous pressure In the edema of venous obstruction, the volume of fluid which escapes into the tissues from the blood stream in a given period of time is proportional to the pressure used to produce the obstruction, and hence, to the capillary pressure If the albumin decreases, as seen in hypoprotein emia of nutritional origin, the decrease in total osmotic pressure causes a drop in the effective driving force and more fluid is lost to and held in the extracellular spaces

Capillary pressures probably vary greatly in the different organs and tissues However, these variations are apparently balanced by cor responding variations in capillary permeability so that continuous fluid exchange between the tissue spaces and the blood is maintained When the arterial blood pressure is abnormally low from any cause, this exchange is curtailed or entirely suspended, as for example, in shock Probably some organs are affected in this manner to a greater degree than others The liver, for example, has normally a very low capillary blood pressure when compared to other organs, and it is possible that diminished tissue fluid exchange within it may so impair chemical processes within the liver cells as to be a factor in rendering this pathologic condition progressive

Plasma Protein Concentration The normal plasma protein con centration is rather constant at about 7 grams per 100 cubic centimeters of plasma, of which 4 1 grams are albumin and 2 7 grams globulin, and 0 27 gram fibrinogen Since albumin is responsible for 80 per cent of the total osmotic pressure, and decreases in serum protein usually affect the albumin fraction more than the globulin, the retention of fluid and edema seen in hypoproteinemia refers primarily to hypoalbumin emia.

Retention of fluid in the interstitial spaces begins with the first dim inution of serum protein and progresses steadily as the protein con tinues to fall, although this retention may not be evident at first The accumulation of fluids in the interstitial spaces without gross visible edema is often described as *latent edema*. This latent edema is an important consideration in the management of gastrointestinal surgical patients It may be the reason for a malfunctioning gastrojejunostomy, or the reason for dehiscence Edema in hypoproteinemia seems to appear rather suddenly when the protein concentration reaches a certain so-called critical level, but this is merely the level at which the accumulation of fluid becomes grossly evident. The critical level of

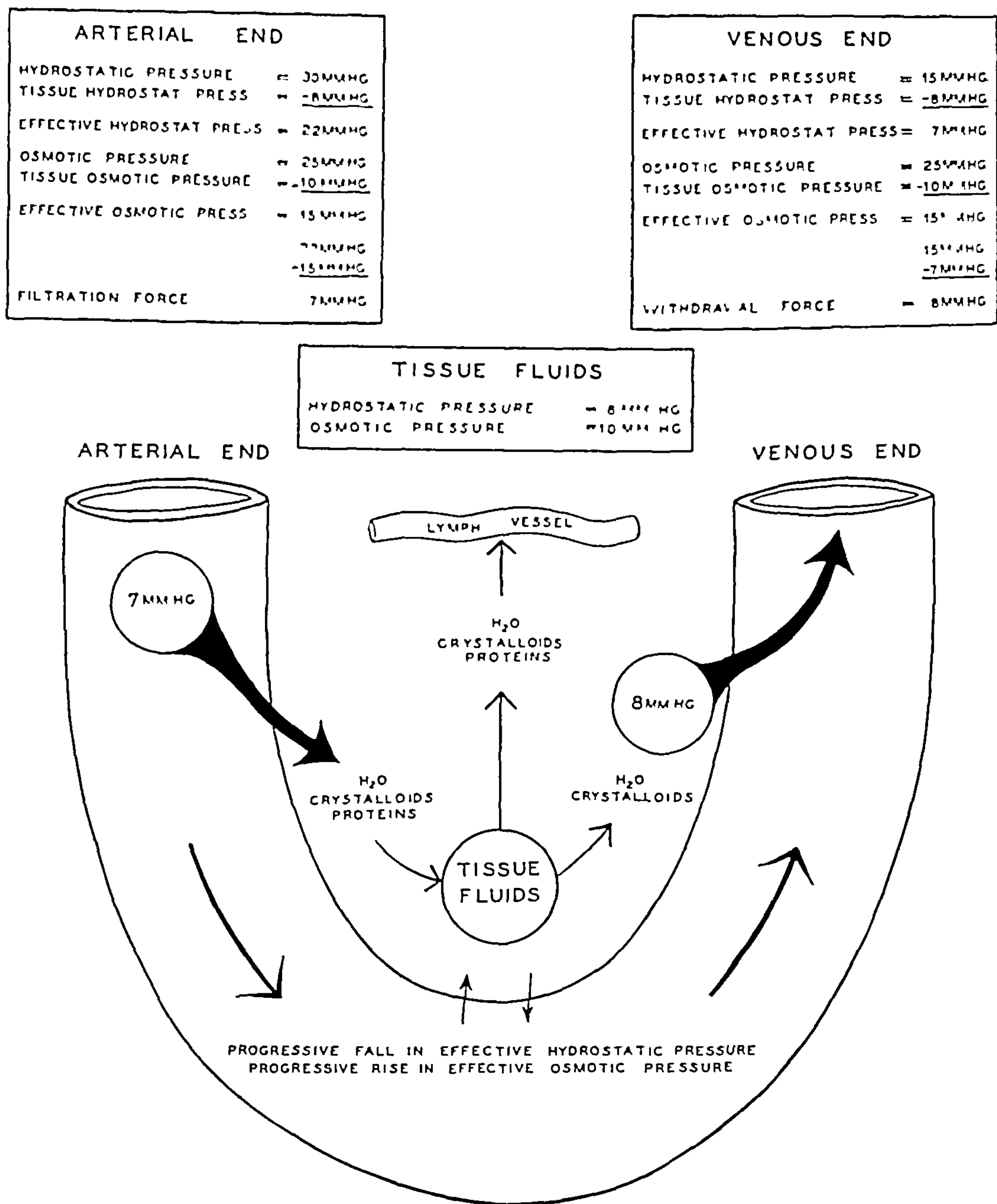


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is possible to estimate the protein content Numerous laboratory procedures have been developed for the determination of the protein content by finding the specific gravity of blood, serum and plasma Barbour and Hamilton in 1924, described a method for determining specific gravity of liquids based on the principle that the time required for a drop of a certain volume to fall a fixed distance through a liquid is governed by the density of the drop and other easily fixed and controlled factors Another specific gravity method is the copper sulfate technique of Phillips *et al* The technique used herein consists of letting drops of plasma or whole blood fall into a graded series of solutions of copper sulfate of known specific gravity, and noting whether the drops rise or fall in the solutions The heavier drops fall, the lighter rise during the first 15 or 20 seconds of contact of the blood or plasma with the copper sulfate solution

Permeability The effective filtration pressure is not the entire capillary pressure but the difference between the latter and the hydrostatic pressure in the tissues about the capillaries, the "tissue tension" Similarly, the effective reabsorptive force is not the entire colloid osmotic pressure of the blood serum, but is the latter minus the colloid osmotic pressure of the interstitial fluid surrounding the capillaries Independently of the balance between these two opposed forces, the permeability of the capillary wall may change However, any increase of permeability favors the movement of fluid in only one direction, namely out of the vessels, because the change of permeability affects only the colloids of the blood and not the crystalloids which are already freely diffusible across the capillary wall Increased vascular permeability permits the colloids to escape from the medium of higher concentration, the serum, to the medium of lower concentration, the interstitial fluid, thereby reducing the effective reabsorptive colloid osmotic pressure which is the difference in colloid osmotic pressure on the two sides of the capillary wall

As Peters points out there is a natural tendency to conceive of the permeability of the capillary membrane as simply a degree of porosity, whereas permeability depends upon not only simple porosity, but also the electrical charges upon the membrane, the miscibility and solubility of the substances of which it is composed with reference to the water and solutes in the adjacent liquids and the chemical reactions which may take place between the substances in the membrane and the substances in the liquids to which it is exposed

Even the simplest living membrane has a busy and complicated task, for it must preserve a differentiation of chemical *composition of the*

protein for the appearance of edema has been stated to be 5 5 per cent A great deal of individual variation is frequently seen It might be wiser to consider 3 5 grams of albumin as the critical level for edema and to disregard the total protein value Youmans in his studies on nutritional edema found a reduced albumin fraction but a total protein within normal limits Repeated studies have proven the fallacy of interpreting the total protein values as an index of hypoproteinemia Other factors which interfere with evaluation of hypoproteinemia by gravimetric determinations of quantity of serum protein in the plasma are dehydration, hyperglobulinemia, contraction of blood mass with decreased protein values, and early variations in hydration as is seen in patients on parenteral therapy

Surgical patients with hypoproteinemia are often dehydrated, hence laboratory determinations will show normal serum protein values although blood volume estimations reveal a low total circulating protein content Patients with dehydration and hypoproteinemia, therefore, seem to be in "the blue" but may actually be in "the red" This difference is elicited when the plasma volume is restored by therapy with crystalloid solutions, especially salt Jones and Eaton have recorded the pernicious effect of salt

Tissue elasticity is one of the controlling factors in the development of edema In emaciation, the loss of turgor and elasticity of the subcutaneous layer impairs the integrity of the capillary endothelium Perhaps the appearance of edema at higher serum protein levels in emaciation can be explained by the above factor

Loss of electrolytes without corresponding loss of proteins, e g, intestinal obstruction and fistulae, causes dehydration of the tissues Loss of proteins without corresponding loss of electrolytes, e g, in profuse drainage from an empyema cavity, causes hydration of the tissues which often becomes manifest in the form of edema The former disturbance has more serious effects In the case of empyema with edema of the lower extremities from protein loss, one or both of the upper extremities may show edema also If only one of the upper extremities is edematous, it is likely that the unilateral involvement will be found in the extremity on the same side as the thoracic disease and is due to the greater immobilization and dependency of this limb as compared with that of the other side

The amount and type of proteins present in the plasma are important factors in determining the viscosity of the blood Globulin is more viscous than albumin, fibrinogen constitutes about 12 per cent of the globulin fraction of the blood Knowing the viscosity of the blood, it

isotonic solutions of the two substances are dialyzed against each other, salt and water will at first pass into the dextrose solution This accounts for the dehydrating effect upon the tissues of dextrose solutions administered intravenously and the mechanism by which it draws off cerebrospinal fluid into the circulating blood, thereby reducing intracranial pressure These effects are, however, necessarily temporary because dextrose is inherently diffusible and ultimately loses its transient osmotic advantage by becoming distributed equally between the blood and the extravascular fluids

Only recently has there been any objective knowledge concerning the rates at which water and solutes move about within the water soluble portion of the body With the advent of tracer techniques, it has been possible to determine the rate at which substances move about in the water soluble area and the different permeabilities of various membranes These studies indicate a rapid diffusion of water throughout the body therefore, a great permeability of all membranes of the body to water as well as an excellent efficiency of the capillary bed The curve obtained implies that the fast membrane is the capillary wall, the slow membrane the cell wall Calculations indicate that approximately 75 per cent of the water of the blood passes through the capillary wall every minute

Osmotic Action of Wet Dressings That hypertonic wet dressings applied to open wounds exert only a temporary osmotic action has been shown experimentally by Taylor He found that the solution rapidly loses its hypertonicity, largely by diffusion of its salt (or glucose) into the wound The innermost layers of the gauze dressing are most affected in this manner If there is the least bit of bloody ooze from the wound, the two inner layers of gauze quickly become isotonic, therefore, the hypertonic solution becomes entirely ineffective in extracting fluid by osmosis, its main purpose This loss of hypertonicity occurs with sodium chloride and with glucose In the case of magnesium sulfate it is less marked, but still quite appreciable, amounting to 14 per cent in the first hour Fluid withdrawn from the wound is water, not serum, it comes only from the superficial tissues and amounts to 1 2 to 1 5 cubic centimeters per hour per square inch of wound surface Taylor states that the therapeutic value of this effect of the hypertonic wet dressing is questionable

According to Peters, the selective properties of living membranes and the complexities of the media between which they are interposed influence the distribution and motions of ions between the cells and the extracellular fluids in such an enormous variety of ways that it is

two fluid media which impinge upon its opposite faces, yet permit easy transfer in both directions of a great variety of substances in the interests of nutrition, functional activity and excretion Some membranes have polarized, that is, irreversible permeability, for example, dermal membranes in general, which permit diffusion in only one direction, yet their function is quite as complicated as that of the membranes which are permeable in both directions

Certain membranes afford free passage to all solutes except large colloids such as proteins and lipoids The simple endothelium of the blood and lymph capillaries, serous surfaces and glomeruli of the kidney belong to this class Some membranes are impermeable not only to colloids but also to particular electrolytes As an example, the limiting membrane of the red blood cell may be mentioned The red cell contains much more protein (hemoglobin) than the surrounding serum, and since the membrane is impervious to protein, a much greater osmotic pressure in the cell than in the serum would be the result if it were not for the fact that the cellular envelope happens also to have a special impermeability to basic ions By virtue of this double balanced impermeability, osmotic equilibrium between cell and serum is maintained Despite the general uniformity of osmotic pressure within the body, the distinctive inorganic patterns in the various types of cells are preserved by means of special impermeability of the cell boundaries with reference to particular ions Adjustments of deviations of osmotic pressure, therefore, are ordinarily effected chiefly by transfers of water rather than exchanges of salts

Even though a solute can pass through a membrane it may for a time exert an osmotic effect before a state of equilibrium is attained For solutes vary greatly in the speed with which they cross a given membrane This variability depends not only upon properties inherent in the solute but also upon the character of the membrane, the nature of the solvent, and the nature of other solvents present Dextrose, for example, can diffuse through vessel walls and serous membranes, but its rate of diffusion is far less rapid than that of urea and certain inorganic ions It is because of this difference in rate that dextrose, though a diffusible substance, can produce temporary disturbances of water distribution in the body Even though two solutions have initially the same osmotic pressure, if the solute in one can diffuse more rapidly than the solute in the other, the latter solution acts temporarily as if it actually had greater osmotic pressure than the other Hence it is that even an isotonic solution of dextrose exerts an osmotic action within the body Sodium chloride diffuses more rapidly than dextrose When

of water balance following operation at the suggestion of Appel and Brill They found it a sensitive and reliable index of the state of hydration of the patient Though they consider the mechanism of the test uncertain, they assume that the rate of dispersal of the wheal fluid into the interstitial tissues is inversely proportional to the tissue avidity for water—whether this avidity be due to actual lack of water or to the water of the tissues being "bound" in some way, as for example, by an excess of sodium MacIntyre, *et al*, found marked variations in the results of the test in normal individuals, and did not find it a reliable index of the state of hydration of experimental subjects or of surgical patients Likewise, Casten, *et al*, in the few cases in which they used it, found the McClure Aldrich test not sufficiently accurate as a measure of dehydration

THE PROTEINS

6-8 G-L

Plasma Proteins—Composition and Functions Albumin, globulin and fibrinogen constitute the three major proteins The total protein content of plasma in the normal adult varies from six to eight grams per 100 cubic centimeters, or about 175 to 200 grams of total circulating protein Albumin is the simplest of the three proteins, is most symmetrical chemically and represents 50 to 60 per cent of the total proteins The normal range per 100 cubic centimeters of plasma is 4 2 to 6 2 grams The molecular weight of albumin is approximately 69,000 the colloidal osmotic pressure per gram is 305 millimeters of water, or 5 5 millimeters of mercury Albumin is the major factor for the osmotic pressure and is responsible for 80 per cent of the total The globulin values vary from 1 3 to 3 0 grams per 100 cubic centimeters with an average of 2 7, the osmotic pressure per gram is 1 4 millimeters of mercury Fibrinogen has the largest molecular weight (300,000) and constitutes 4 per cent of the total proteins The values for fibrinogen are given at 200 to 300 milligrams per 100 cubic centimeters This protein is closely linked with those diseases associated with prolonged leukocytosis and protein destruction. The liver is thought to be the most likely site for the formation of fibrinogen

The plasma proteins are particularly stable chemically, physically, and physiochemically in vitro and in vivo, and studies by Weinstein on stored plasma have shown no major chemical alteration in the albumin content after two years of storage at room temperatures In some of the diseases associated with hypoproteinemia or faulty fabrication and utilization of proteins, abnormal forms of albumin or globulin may be produced The serum albumin found in patients with nephrotic syn

impossible as yet to subject these phenomena to anything like rigid mathematical treatment

Properties of the Red Cell Membrane. The chemical pattern of the blood cells is extremely different from that of the blood serum, yet cells and serum have the same osmotic pressure The *cell membrane* of the red blood corpuscle permits the free passage of water and of easily diffusible organic solutes such as dextrose and urea in both directions Among the inorganic ions, it is quite permeable to chloride and bicarbonate, but within certain conditioned limits It is relatively impermeable to protein, for the proteins within the cell differ greatly from the serum proteins outside the cell It is also impermeable to bases In man, sodium constitutes more than 90 per cent and potassium only 3 per cent of the base of plasma, whereas, in the erythrocytes potassium is the predominant base, there being very little sodium *Serum* contains both calcium and magnesium, more of the former than the latter, cells contain no calcium, but do contain magnesium, in fact a larger amount than in the serum This segregation of the bases in the two phases of the blood is attributed to a selective permeability of the cell membrane In some animals, the dog for example, sodium and potassium are more evenly distributed between the cells and the serum

Effect of Acidity and Alkalinity on Permeability· Acidification, however produced, causes both water and chloride to pass into the blood cells Alkalinization has the opposite effect It is highly probable that disturbances of acid-base balance cause similar exchanges of water and chloride to take place between all the other cells of the body and the interstitial fluid Probably there is a close analogy in this and in other respects between the red cell-serum relationship and the tissue cell-interstitial fluid relationship, acidity promoting absorption of interstitial fluid

McClure-Aldrich Test for Body Hydration A functional test (McClure and Aldrich) of the local efficiency of the circulation in an extremity by means of intracutaneous injection of saline solution depends upon the fact that anoxemia produces in the affected part an increase of salt concentration and a relative increase of acidity These two factors greatly increase the absorbability of injected fluids Physiological solution of sodium chloride injected in wheals into the skin is absorbed *more* rapidly than normally, in proportion to the degree of circulatory impairment The normal absorption time is from 40 to 60 minutes In certain vascular diseases and in sudden arterial occlusion, the wheal may disappear in as little as five or six minutes

Hopps and Christopher used the McClure-Aldrich test as a measure

hence, edema ensues In such a case, the edema is not due really to excessive salt administration Another pitfall in measuring total protein is found in those conditions in which the drop in albumin is marked by the rise in globulin fraction, as in severe infections, nephrosis, carcinoma, and Hodgkin's disease

Recent reports by Clark *et al*, show contraction of the blood volume in hypoproteinemia This contraction in blood volume validates the correctness of quantitative fractionation determinations of the plasma proteins Blood volume determinations are likewise necessary to correctly evaluate the degree and significance of hypoproteinemia These authors have attached the term "chronic shock" to subacute or chronic hypoproteinemia

Clinical hypoproteinemia may be *acute, subacute,* or *chronic* in origin Acute protein needs are seen in hemorrhage, secondary shock from trauma, and burns The acute deficit should be replenished immediately by whole blood plasma or albumin Acute deficits as seen in the operating room are poorly tolerated by the patient, therefore, the early replacement prevents circulatory impairment, and the development of shock—a serious handicap to the recovery of any patient undergoing a major surgical procedure The amount of blood lost during operations is frequently of greater magnitude than one tends to realize For this reason, early adequate replacement is important In fact, in no other place in surgery does the proverb "an ounce of prevention is worth a pound of cure" fit better The dose of blood or plasma necessary to correct the deficit is greater than common practice predicates Five hundred cubic centimeters and still more frequently, 1000 cubic centimeters and more are needed The value of large doses of blood and other derivatives given early, adequately and repeatedly in the management or prevention of secondary shock is described by many A complete discussion of this subject may be found in the text of White and Weinstein, *Blood Derivatives and Substitutes*

Clinical hypoproteinemia follows a variety of general causes The four major etiologic factors may be grouped as follows 1 Loss 2 Destruction 3 Inadequate intake, relative or absolute 4 Decreased and defective formation, utilization, absorption and digestion of proteins

Loss of protein may occur through the skin, in exudates, transudates, from the gastrointestinal tract and via the kidney Protein loss from the skin is found in exudative or exfoliative dermatological diseases, in burns, in ulcerations from granulating surfaces, and from sinuses and fistulae A great deal of protein can be lost in 24 hours in transudates

drome contains less than the usual quantity of cystine A nonantigenic form of albumin has been described in severe hypoproteinemia, and a high beta globulin and fibrinogen with a low albumin is found in acute and chronic cholangitis and hepatitis

Important physical physiologic and biochemical functions can be attributed to the plasma proteins These functions are as follows 1 They help to maintain the osmotic pressure of the blood, the blood volume and the fluid exchange between the circulating blood and tissues 2 They exert a functional resistance in the arterioles which influences the amount of fluid which passes through in a unit of time, and thus is a factor in the maintenance of blood pressure 3 They are amphoteric, and aid in the regulation of the acid-base balance by acting as acids to combine with bases 4 They yield trephones essential to the nourishment of tissue cells 5 They are an important source of protein to the body when there is a negative nitrogen balance

Hypoproteinemia—Production· Hypoproteinemia implies a decrease in the plasma proteins This deficit can be measured by various laboratory procedures A decrease in plasma protein rarely represents an isolated deficit, but usually indicates the presence of general protein deficiency

Though the measurement of plasma protein content is of clinical value and theoretically important in measuring acute and chronic protein deficiency, there are many pitfalls which must be considered The methods used for determining the proteins may help to explain the discrepancies which appear The methods used include the following tests gravimetric, colorimetric, refractometric, specific gravity or density, Kjeldahl nitrogen, electrophoresis, and ultracentrifugation Any method which only measures the total protein content of the blood plasma is inaccurate from the first, because most of the conditions associated with hypoproteinemia reflect changes in the albumin fraction, and rises in globulin are frequently seen Hence, fractionation of the protein fractions is necessary Another reason for inaccurate interpretations from serum protein values in the measurement of hypoproteinemia lies in the associated presence of dehydration The decreased plasma volume of dehydration increases the value for protein concentration and masks the true deficit present It is only after correction of the dehydration with fluids that the true condition is found The combination of dehydration and hypoproteinemia sometimes explains the sudden appearance of edema in a patient who has a serum protein level of 7 0 grams After administration of enough fluid and salt, it becomes evident that the true serum protein value is below edema levels, and

repeatedly has been able to achieve positive nitrogen balance in post operative patients with varied surgical procedures by an adequate parenteral intake of nitrogen and carbohydrate Clinical experience and metabolic studies do teach us that the healthy individual undergoing stress loses a larger amount of nitrogen as compared to the chronically ill patient, who has been on an inadequate diet before similar surgical procedures This controlling effect is probably a conserving mechanism on the part of the body to prevent unusually large deficits from developing Protein deficiency from increased metabolism of pyrexia, sepsis, and hyperthyroidism has long been known clinically as a factor in the prognosis of illness with these manifestations A decreased protein level in the blood with hyperthyroidism is practically a pathognomonic sign of this disease

Protein deficiency may also result from a *reduced ability* to *digest absorb, utilize,* or *form proteins* In carcinoma of the jejunum, tuberculous enteritis, intestinal fistulae, ulcerative colitis, sprue, regional ileitis and severe hypoproteinemia, there is an impaired digestion, absorption and utilization of protein Faulty formation and fabrication are seen in acute and chronic hepatic disease, pancreatic disease, and upper gastrointestinal malignancy Ariel has reported the following findings in carcinoma of the stomach. The presence of a lesion in this area prevents fabrication and utilization of ingested or parenterally fed protein when the liver is without metastases If the lesion is removed surgically, the patient can then correct this inability of utilization and fabrication

Absorption and utilization likewise depend upon the source and state of nutrient supplied For example, proteins of animal origin are more readily digested and absorbed than those obtained from plant origin And the human gastrointestinal tract can completely utilize the thiamine present in fresh yeast as well as that in dried or boiled yeast. The only true intake of nutrient, therefore, is the utilizable content of food rather than the total content of food as described in tables on nutrition

The physiologic development of hypoproteinemia may be compared to the cycle of secondary shock In the first instance, hypoproteinemia will eventually produce greater hypoproteinemia In the case of shock oligemia causes changes in capillaries and organs, which eventuate in greater oligemia and irreversible changes in the vital organs and capillaries During the development of chronic protein deficiency, the mobile or labile proteins are first withdrawn or depleted to a greater extent Then the visceral proteins are drawn up to maintain the plasma proteins Eventually the plasma proteins are depleted producing recog

Clinical examples are represented by peritonitis, tuberculosis, cellulitis and abscesses of the peritoneum or pleura, pleural effusions after thoracic surgery, sudden arterial occlusions with subsequent gangrene, and deep venous obstructions and postphlebitic edema

The gastrointestinal tract can be the source for loss of protein either acutely or chronically Diarrheas produce large deficits in body protein, acute and chronic bleeding likewise deplete blood and tissue proteins A review of the following conditions shows the many clinical conditions of the gastrointestinal tract which may be responsible for the loss of protein by this channel chronic diarrheas of amebiasis, sprue syndrome, nonspecific colitis, bacillary dysentery, regional enteritis, severe hypoproteinemia, bleeding as seen in peptic ulcers, carcinoma of the colon, ulcerative colitis, polyps and severe hemorrhoidal disease

In albuminuria, nephritis, toxicities, nephrotic syndrome, infection and pregnancy, albumin is lost through the kidneys, as much as 30 to 90 grams of albumin per 100 cubic centimeters of urine is described The most pronounced derangement in serum protein as well as tissue proteins is shown by patients with chronic nephrotic syndromes

Low intake is an important factor in the production of hypoproteinemia Inadequate intake is either relative or absolute, voluntary or forced It is seen in patients with vegetarian habits, peculiar appetites, stylish reducing fads, and war famine Absolute low intake is noticed in preoperative and postoperative patients, those with obstructive gastrointestinal lesions, and in anorexia nervosa Weinstein reported a severe case of hypoproteinemia in a patient who had been told 20 years before to avoid all proteins because she had kidney trouble Severe malnutrition was seen during and after World War II from food starvation The inmates of Dachau were an example of severe depletion due to low intake Reports describe the following diet as characteristic of these inmates: ersatz coffee for breakfast, one slice of hard dried bread with a cup of thin broth for lunch, ersatz coffee with or without bread for supper, and on rare occasions a small portion of potatoes, or like carbohydrate food, for the evening meal

Diseases and injuries lead to an *increased destruction* and an *increased demand* of certain nutrients This represents a part of the "alarm reaction" described by Selye The increased loss of nitrogen seen after fractures, operations, and traumatic injuries has been described as "toxic" loss of protein Many authors feel that this toxic loss is unpreventable and cannot be controlled or corrected Opposed to this theory is Werner, who is of the opinion that the chief reason for postoperative negative nitrogen balance is inadequate intake Weinstein

nizable hypoproteinemia Severe and profound protein depletion terminates in an irreversible stage or degeneration in the tissues and vital organs and death may ensue

The clinical manifestations of hypoproteinemia can be grouped under two main headings 1 Increase in manifestations or functions 2 Decrease in function or organs Figure 24 shows the clinical manifestations of hypoproteinemia under the two previously described headings of increase and decrease

Relationship of Blood Proteins and Tissue Proteins The food proteins yield amino acids which are absorbed from the intestinal tract and these amino acids are synthesized in the liver and elsewhere into plasma proteins The plasma proteins, both hemoglobin and plasma protein, of which there is a considerable reserve, supply the protein requirements of the body cells

Body protein stores protein production and protein wear and tear, or protein loss are in nicely balanced or steady state—dynamic equilibrium These proteins can pass readily from plasma into cells or from cells into plasma without loss of nitrogen. Whatever our concept of protein molecules, and their passage through cell surfaces, we are forced to the conclusion that protein does pass through cell surfaces readily as a part of normal protein metabolic exchange The term "protein pool," suggests that within the total mass of body protein there is a fluid interchange between the proteins in cells, in reserve stores, in production, in utilization and circulation

Hemoglobin in its production may derive in part protein from plasma protein, but hemoglobin contributes to the "protein pool" for exchange only when the red cell wears out or is destroyed Thereafter, there is separation of the iron, and a complete loss of the pigment radical to the liver and bile

"The liver is the master organ for various protein metabolic activities —it stores proteins, it makes proteins (fibrinogen, prothrombin and probably either globulin or albumin) and it aggregates amino acids and other nitrogenous materials coming from the gastrointestinal tract into proteins Whether these new formed proteins may be liver protein first and subsequently proteins for exchange and distribution (plasma proteins) is beside the point"

The complexity of the mechanisms involved in the regulation of the blood proteins is emphasized by Casten, *et al* who point out the inadequacy of the simple 'loss and lack" conception which seems to be prevalent Determination of the serum protein level cannot be casually

INCREASE

GASTRIC EMPTYING TIME	WEIGHT (RELATIVE)
TRAUMATIC EDEMA	HEMOCONCENTRATION
WOUND INFECTIONS	SUSCEPTIBILITY TO SHOCK
INJURY TO VISCERA (LIVER)	SUSCEPTIBILITY TO TOXIC AGENTS

DECREASE

INTESTINAL MOTILITY
WOUND HEALING
UTILIZATION AND ABSORPTION PARENTERAL FLUIDS (NACL)
URINARY EXCRETION
UTILIZATION OF PROTEINS
DEFECTIVE UTILIZATION, ABSORPTION, FORMATION, AND STORAGE OF PROTEINS
PERIPHERAL CIRCULATORY EMBARRASSMENT
PITTING EDEMA OF TISSUES
BLOOD PROTEINS 6–5% OR LESS

FIG 24 Hypoproteinemia—Clinical Manifestations

I Increase in Functions

Gastric emptying time	Weight (relative)
Traumatic edema	Hemoconcentration
Wound infections	Susceptibility to shock
Injury to viscera (liver)	Susceptibility to toxic agents

II Decrease in Functions

Intestinal motility
Wound healing
Utilization and absorption parenteral fluids (NaCl)
Urinary excretion
Utilization of proteins
Defective utilization, absorption, formation and storage of proteins
Peripheral circulatory embarrassment
Pitting edema of tissues
Blood proteins 6 to 5% or less

(White, C S and Weinstein, J J *Blood Derivatives and Substitutes*, p 427)

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The complexity of the mechanisms involved in the regulation of the blood proteins is emphasized by Casten *et al* who point out the inadequacy of the simple 'loss and lack" conception which seems to be prevalent Determination of the serum protein level cannot be casually

transposed into quantitative terms of disease or interpreted in quantitative terms of therapy Casten and his co-workers mention a number of facts which indicate the incompleteness of our knowledge of the physiology of the blood proteins 1 The serum protein concentration bears no relation to the nitrogen metabolism of the organism as a whole 2 The body has a great ability to regenerate serum proteins regardless of the initial nutritional state 3 When there is a prolonged, marked loss of protein the serum proteins do not continue to fall, but remain at a constant low level, this suggests a controlling mechanism of some kind 4 Several times in acute appendicitis, these authors have observed a depressed ability of the body to regenerate serum proteins, even in *patients apparently in a normal nutritional status*, *in certain fulminating* infections a serum protein deficiency may develop very quickly, even if ample protein is available 5 There is some evidence that the hypoproteinemia produced by malnutrition may be due to damage inflicted on the serum protein regenerating mechanism rather than to mere restriction of protein intake 6 In severe liver disease the ability to regenerate serum proteins may be lost regardless of excess administration of protein

There appears to be some degree of reciprocal equilibrium between the plasma proteins and the tissue proteins, so that in times of need one can draw upon the other The conversion of plasma proteins into tissue proteins is occurring continually throughout the body, but not necessarily the reverse process It seems that certain reserves are earmarked for the support of the plasma protein level, whereas other tissue proteins do not have this function or power

Starvation or a low protein diet markedly reduces the protein content Ravdin states that the tissue stores of mobilizable or labile protein may be much depleted before there is any extreme fall in the blood protein concentration, and cites evidence that intravenously injected plasma protein is utilized first to replenish these protein stores Such transfused plasma protein definitely reduces the susceptibility of the liver and other viscera to injury, in the liver it probably acts by displacing fat and sparing the liver cell proteins Ravdin advises a combined high protein, high carbohydrate diet pre- and postoperatively as a means of sustaining the functional integrity of the liver

It is now generally agreed that there is no critical level of serum proteins at which edema appears Casten, *et al*, recognize rather a "correlation level" of serum proteins with reference to tissue tension They point out that the albumin and globulin not only are chemically different, but also bear no quantitative relation to each other The

albumin globulin ratio, therefore, has no intrinsic significance, each substance being affected by different conditions and the concentration of one constituent in the plasma having no effect on the concentration of the other In hypoproteinemia, the globulin concentration is not commonly decreased Each gram of albumin is responsible for an osmotic pressure of 5 5 millimeters of mercury, so that the total serum albumin (3 5 to 5 grams) exerts an osmotic pressure of 23 millimeters of

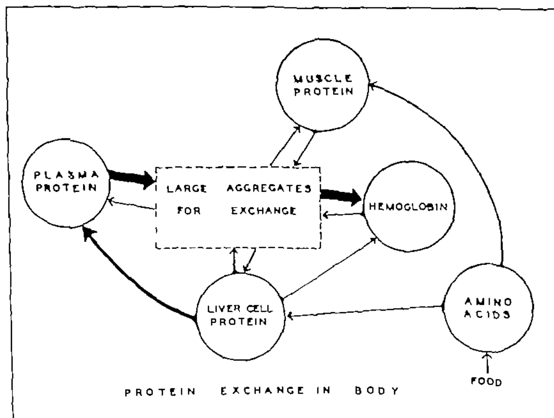


FIG. 25 Protein Exchange in the Body Protein Give and Take. (Whipple, G H *Am J Med Sc* 196)

mercury Each gram of globulin is responsible for an osmotic pressure of 1 4 millimeters of mercury the total serum globulin (1 5 to 2 6 grams) exerts an osmotic pressure of 3 millimeters of mercury In the production of edema, therefore, variations in the globulin concentration are relatively insignificant Seldom will edema be present if the serum albumin is over 3 grams per 100 cubic centimeters regardless of the globulin level (Figure 25)

The loss of tissue proteins which will produce a reduction of 1 gram in the total circulating serum albumin has been estimated as 30 grams of body proteins By applying this finding one may calculate the body loss for each gram of reduced albumin The following formulae will give the weight loss corresponding to the blood albumin deficit

grams albumin deficit per 100 cc serum ×
35 (plasma is 5 per cent body weight, or 3 5 Kg or 3500 cc) ×
30 (estimated depletion of tissue protein for each 1 0 Gm plasma albumin deficit) =

Estimated Tissue Deficit

estimated tissue deficit ×
5 (Gm nitrogen muscle protein 80 per cent water) =

Grams Body Weight Deficit

grams body weight deficit –
454 (Gm per Lb) =

Pounds Body Weight Loss

Example
1 Gm albumin deficit × 35 × 30 = 1050 Gm tissue deficit
1050 × 5 = 5250 Gm Body Weight Loss
5250 divided by 454 = 11 5 Lb Body Weight Loss

NITROGEN BALANCE

In the normal individual on an adequate average diet, there is a balance and equilibrium between protein nitrogen intake and output It has been shown that a 70 kilogram man on 1 gram of protein per kilogram of body weight will lose 10 grams of nitrogen per day Ninety per cent of the end products of nitrogen metabolism are excreted in the urine, and about 10 per cent in the feces A negative nitrogen balance exists when more tissue protein is broken down and lost than is assimilated The negative balance period continues during the stage of recovery until the amount assimilated covers the deficit When the body cells attain optimal protein content, they lose their power to attach additional protein, and nitrogen equilibrium is again established

In the normal individual in nitrogen equilibrium, the amino acids are required for the restoration of tissue protein, for the building of hemoglobin or plasma proteins, for the manufacture of hormones, and for the intestinal secretions and enzymes Those not utilized are broken up and deaminized Of the retained, 58 per cent is transformed to carbohydrates and used as such, while the nitrogenous end products are excreted in the urine Once nitrogen balance is established, additional feeding of protein leads to increased metabolism and the establishment of nitrogen equilibrium at higher levels, because the body has a limited ability to store proteins

Each gram of nitrogen excreted in the urine or feces represents 6 25 grams of body protein utilized The figure 6 25 is obtained from the fact that all body protein contains 16 per cent nitrogen (100 divided by 16) Grams nitrogen are converted to grams protein by multiplying by

6 25 One pound of body weight represents 15 grams of body nitrogen

General Metabolic Considerations of Proteins Each day of life of an individual involves a constant turnover of body proteins, and a definite amount of wear and tear which has to be repaired, from dietary intake, protein reserves and tissues The daily amount of protein metabolism is dependent upon the level of tissue protein saturation and protein stores, the energy or caloric requirements, and the availability of these as either carbohydrates or fats, and lastly, the physiological demands of growth, lactation, illness, injury, convalescence, and diseases associated with protein abnormalities

We are all familiar with the general concept of the caloric needs of the body—the energy requirements must be met This is accomplished by the three essential nutrients—proteins, carbohydrates and fats These three nutrients are interchangeable as far as calories are concerned, and both fats and carbohydrates are "protein sparing" These latter two differ in their "protein sparing" capacity, for carbohydrates have a specific protein sparing action that is independent of the energy metabolism. If fat is the sole source of calories, it is difficult to achieve and establish nitrogen equilibrium

In malnutrition, there is a constant relationship between the protein needs and energy needs During the early stages of starvation in a healthy individual, it is estimated that 13 per cent of the caloric needs are met by burning body protein and the remainder from fat and carbohydrate As the body is depleted of caloric material in starvation, the protein catabolism is also lowered so that the individual's protein metabolism reaches a "starvation minimum" This point is only seen when the total food intake is seriously decreased If at starvation levels only carbohydrates or fats are fed without concomitant amounts of proteins, the protein needs increase in spite of the so-called "protein sparing" effect of these two nutrients and greater tissue protein deficiency will follow It is necessary to give three times the starvation level of nitrogen output to put patients back into nitrogen equilibrium On the other hand, if a sufficient amount of nitrogen is supplied with an over all lower total caloric intake, nitrogen equilibrium will be attained, but the body will still lose weight by the burning up of fat This phenomenon of nitrogen equilibrium without energy equilibrium was demonstrated by Voit

The quantity of carbohydrate needed to spare proteins in patients requiring parenteral therapy is being discussed in medical literature today Elman is of the opinion that minimal caloric requirements are all that need be met in the immediate postoperative period, others

describe 100 grams as the amount of dextrose required for maximal protein sparing in the normal adult. Wren and Sachar concluded that the over-all incidence of ketonuria decreased after operation under spinal anesthesia when the carbohydrate intake was from 150 to 200 or more grams per day The two-fold purpose of parenteral dextrose is said to be achieved with the administration of 200 to 350 grams of dextrose well placed during the 24-hour period

Negative nitrogen balance is found following surgical or accidental tissue damage, and for reasons as yet not completely understood, injury causes an excessive catabolism of body proteins There is an excellent review of protein metabolic response to trauma in an article by Braasch The objective of modern protein therapy is to restore a negative nitrogen balance to a positive one, and then, as the protein stores of the body are replenished, to nitrogen equilibrium

In studying the nitrogen metabolism in a patient, one must study chemically the quantitative differences between all proteins ingested orally or parenterally, and the total protein losses in urine, feces, skin, or by abnormal routes The following chemical studies are necessary to determine accurately nitrogen metabolism 1 Nitrogen content of the diet, oral or parenteral 2 Total nitrogen, urea, uric acid, creatinine, and alpha amino nitrogen of the twenty-four hour urine specimen 3 Total nitrogen of the twenty-four hour feces 4 Nitrogen content of any abnormal losses of fluid or protein. Example biliary drainage, intestinal fistulae, serum from wounds 5 Hemoglobin, hematocrit, red blood cell count, total protein, albumin and globulin ratio, alpha amino nitrogen, urea and nonprotein nitrogen daily determinations 6 Blood volume and total circulating plasma proteins should be determined if the materials are available

CLINICAL PREOPERATIVE AND POSTOPERATIVE PROTEIN DEFICIENCY

Preoperative protein deficiency, as shown by total protein and hematocrit determinations in surgical patients, is far more frequent than one might suspect A review of 246 surgical cases by Weinstein showed that 23 1 per cent had total protein levels below 6 grams per 100 cubic centimeters of plasma and that 23 5 per cent had hematocrit values under 38 These figures indicate a diffuse deficit of tissue, plasma and hemoglobin proteins in these patients The following listing of patients, with varied surgical diseases, showing hematocrits below 38 and total proteins below 6 grams per cent gives the incidence of these deficiencies

Disease	*Per Cent with Hematocrits Below 38*	*Per Cent with Total Proteins Below 6 Grams*
Hemorrhoids	27 2	1 1
Cellulitis of leg	34 8	34 8
Inguinal hernia	1 6	8.3
Acute appendicitis	2.0	16 0
Acute cholecystitis	12 5	16 6
Chronic cholecystitis	13 0	8 7
Peptic ulcer	25 0	33 3
Gastric carcinoma	37 3	33.3
Intestinal obstruction	19 4	19 0
Lung abscess	62 5	50 0
Carcinoma of colon	38 0	24 0

Jones and Eaton found hypoproteinemia to be common among surgical patients with gastrointestinal diseases, and Mulholland found it in all patients with decubitus ulcers

Postoperative protein deficiency is due to inadequate preparation, inadequate intake, increased catabolism, abnormal losses of protein through abnormal routes (skin, fistulae, sinuses), and inadequate caloric intake Recent studies by Weinstein, with carbohydrate as the sole source of calories after surgery, show that 1200 calories per day when given as invert sugar will prevent ketosis, minimize excessive weight loss, prevent serious serum protein decreases, and limit nitrogen output Gastric resections studied in this series excreted between 8 and 10 grams of nitrogen per day—an amount commensurate with normal nitrogen output for a healthy, nontraumatized individual

Frequently there is a direct relationship between the extent of the abdominal operation and the postoperative hypoproteinemia. Many patients undergoing intestinal resections starve for three to four days after surgery As much as a pound of body weight may be lost per day in the immediate postsurgical period Many groups studying burns describe a 3 0 to 5 0 gram decrease in serum proteins in severe cases Meyer and Kozol found a 25 per cent plasma protein drop in patients undergoing surgery for intestinal obstruction and carcinoma of the colon Further proof of protein deficiency postoperatively is seen in figures from cases studied by Weinstein 11 of 20 cases of inguinal hernioplasty lost 0 45 gram of protein in nine days during the first five postoperative days when the deficit is greatest, 13 cases revealed a 0 53 gram decrease in total protein, and 12 had a 0 49 gram albumin deficit A 2 2 per cent drop in hematocrit occurred in these cases After

describe 100 grams as the amount of dextrose required for maximal protein sparing in the normal adult Wren and Sachar concluded that the over-all incidence of ketonuria decreased after operation under spinal anesthesia when the carbohydrate intake was from 150 to 200 or more grams per day The two-fold purpose of parenteral dextrose is said to be achieved with the administration of 200 to 350 grams of dextrose well placed during the 24-hour period

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of the initial plasma protein concentration Volume for volume, plasma transfusion introduces protein approximately twice as fast as transfusion of whole blood Scudder mentions the fact that proteins in preserved blood do not undergo appreciable alterations in chemical structure, for their electrophoretic pattern remains unchanged

Mahoney, *et al*, point out that in postoperative hypoproteinemia, as long as food cannot be taken, large amounts of plasma must be given by transfusion, as some of the protein thus given is utilized and consumed in the body metabolism It is usually impossible to restore the normal protein concentration by this means in such cases, but one can maintain the proteins above a "critical" level until food can be taken

Likewise, Casten *et al* have found that in many cases it is impossible to replenish the serum proteins, even with repeated massive transfusions They acknowledge that therapy must, of necessity, be symptomatic and haphazard at present in such cases Fortunately, most patients have no serious defect in the serum protein regenerating mechanism, even though the latter is unknown Administration of protein by mouth is best if it is practical. Transfusions of blood or plasma are effective only if large in amount and frequently repeated After transfusion of 1000 cubic centimeters of blood or plasma, the serum protein level may rise only 0 2 to 0 4 gram, and fall again in 24 hours to the initial level As Caston *et al* observe, the therapy of hypoproteinemia rests on an insecure foundation

The treatment and correction of protein deficiency require a planned nutritional program which embodies enough blood to correct anemia and hypoproteinemia, an adequate quantity of proteins, vitamins, carbohydrates and calories either by oral or parenteral routes to maintain daily protein equilibrium and an excess of these to restore tissue depletion

The quantity of blood needed to correct anemia is evaluated from the hematocrit level One hundred cubic centimeters of blood is given for each point of hematocrit below the desired level of 42 The grams protein needed may be calculated from the weight loss For each pound of body weight loss, 15 grams of nitrogen are destroyed, or 90 grams of body protein

If parenteral therapy is necessary to replace protein depleted tissues, hydrolysates administered by vein, skin or muscle are indicated. Plasma protein hydrolysate prepared from bovine blood has been used for some time by Weinstein, as a source of parenteral protein in surgical patients This preparation can be given rapidly with a minimum number of reactions Nitrogen balance studies in various surgical patients by Wein-

cholecystectomy, a drop of 0 5 gram of protein and a 6 point decrease in hematocrit was seen Gastrectomies developed a 1 gram protein decrease and a 20 per cent hematocrit deficit Individual case analysis frequently shows larger losses

Assessing the Protein Deficiency Before or After Surgery: The following program should be employed to evaluate the presence or degree of protein deficiency in surgical patients 1 Medical history and physical examination 2 Dietary history determine the adequacy of the diet 3 Estimation of weight loss determine the optimum weight, the observed weight, and calculate the weight deficit 4 Estimation of degree of anemia, and hypoproteinemia This is done by use of the following tests hematocrit, complete blood count, total protein, albumin and globulin ratio, and blood and plasma volumes

In acute depletion the albumin is lost faster than the globulin, and in repair is built up more slowly Repeated serial plasma protein fraction determinations, therefore, give a good estimate of protein depletion In chronic illnesses, plasma proteins fall late Protein deficits thus indicate great tissue depletion. Daily weighings of surgical patients is by far one of the more accurate methods of evaluation of the postoperative nutritional depletion The losses seen after injury may continue for as long as the patient is seriously ill unless special effort is taken to prevent this

CLINICAL MANAGEMENT OF PROTEIN DEFICIENCY

Excellent results are reported by Hill, *et al*, from the use of four times concentrated plasma prepared by desiccation from the frozen state (lyophile plasma) in the prevention and treatment of complications associated with hypoproteinemia such as saline edema, closure of anastomosis stoma, pulmonary edema with retarded wound healing The plasma protein level may not be raised appreciably following administration of concentrated plasma because the depleted storage depots for plasma proteins must be replenished first and may be pictured as absorbing the injected plasma protein in sponge-like fashion In hemorrhage, if the loss of red cells amounts to 60 to 75 per cent of the total, whole blood is required for treatment But in less severe hemorrhage, concentrated plasma has been found to be a good blood substitute

Scudder emphasizes the difficulty of increasing the plasma protein concentration by plasma transfusions In 20 cases in which 500 cubic centimeters of plasma were injected, the average increase in the plasma protein level was only 2 5 per cent that is, presumably, 2 5 per cent

Composition of the Interstitial Fluid Qualitatively, interstitial fluid appears to be an ultrafiltrate of serum Peters believes that the available data permit the hypothesis that the tissue cells contain practically no sodium or chloride, potassium constituting nearly all of their base, whereas the interstitial fluid contains considerable amounts of sodium and chloride, but only a small amount of potassium, and is homogeneous throughout the body The different *base radicals* are distributed between the cellular and interstitial phases of the tissues in about the same proportions in which they are distributed between red blood cells and serum The interstitial fluid, which makes up only one-fifth of the body weight, contains most of the chloride and sodium of the body Since the intra and extracellular fluids are in osmotic equilibrium, any change in water content (or base concentration, for the water content is always proportional to the latter) of one of the phases must be equalized at once by a transfer of water from one phase to the other

In drawing conclusions as to water and salt exchanges on the basis of chemical analysis of the blood serum, the effects upon the composition of the blood of such transfers of water between cells and interstitial fluid must be taken into account Contact of the intracellular phase with the environment is effected only through the interstitial fluid The same is true of intercommunication between different cells

Osmotic Properties of Interstitial Fluid Although sodium is present only in the interstitial fluid, any change in the concentration of sodium disturbs osmotic pressure relations and must, therefore, be followed by a compensatory movement of water across the tissue cell membrane. This shift of water is such that it tends to mitigate the change in the composition of the interstitial fluid For example, if sodium chloride is administered without water, the added salt remains in the interstitial fluid, for the tissue cells normally admit (and contain) little or no chloride or sodium But because of the increased osmotic pressure of the interstitial fluid, water moves from the cells into the interstitial fluid until the osmotic pressures are again equal The quantity of water shifted is not sufficient to restore the exact original osmotic pressure of the interstitial fluid, for this would leave the cells with a relative deficiency of water, and therefore a higher osmotic pressure than the interstitial fluid Instead, the cells permit the loss of somewhat less water than this, so that the excessive osmotic pressure of the interstitial fluid is reduced and that of the cells themselves is increased, until the two come into equilibrium

The final result is a moderate and uniform increase in the osmotic

stein have shown that it achieves positive nitrogen balance, prevents weight loss, and also prevents depletion of plasma proteins and hemoglobin Three thousand cubic centimeters of a 5 per cent plasma protein hydrolysate plus 5 per cent dextrose (Baxter Laboratories, Incorporated) is the daily amount required for total parenteral alimentation This amount of nutrient gives the patient the following Water, 3000 cubic centimeters, Salt, 6 7 grams, Protein as amino acids, 150 grams, Glucose, 150 grams, Total calories, 1200 Caloric intake may be increased by adding greater quantities of glucose or invert sugar to the 5 per cent plasma protein hydrolysate

"Protein feeding should be given intravenously until mouth feeding can be tolerated and should be continued as a supplement until oral feeding with or without gavage has been established at a sufficient level, not only to maintain the patient in nutritional equilibrium but also to restore at a rapid rate all tissues that have been depleted " The use of parenteral blood and protein solutions with glucose will not only shorten convalescence in surgical patients, but will also save lives

INTERSTITIAL FLUID

Volume of the Interstitial Fluid · Tissue cells and interstitial fluid cannot be separated for direct analysis of each, as in the case of the blood cells and serum Therefore, the volume and composition of interstitial fluid are not known with accuracy It is estimated that approximately 15 per cent of the total body weight consists of interstitial fluid This is equivalent to 15 liters This mass of fluid is separated from the fluids within the cells by a barrier impermeable to certain chemical substances The quantity of interstitial fluid varies in different tissues, the approximate average values for the various organs and tissues, as estimated by Peters from the available data, are given in Table XV

TABLE XV

PROPORTION OF INTERSTITIAL FLUID IN VARIOUS TISSUES

Skin	43%
Muscle	13
Kidney	57
Lung	49
Liver	37
Spleen	35
Pancreas	32
Intestine	28
Adrenal	24

(Peters, J P *Body Water*, page 113)

TABLE XVI

ELECTROLYTE COMPOSITION OF PLASMA
(In milliequivalents per liter)

	Base	Acid
Na	142	—
K	5	—
Ca	5	—
Mg	3	—
HCO_3	—	27
Cl	—	103
HPO_4	—	2
SO_4	—	1
Organic Acids	—	6
Protein	—	16

(Fine, J *Care of the Surgical Patient* page 19)

intake is applied mainly to the maintenance of extracellular fluid. The extracellular fluid volume is mainly contracted by the kidney which removes water with respect to the maintenance of normal extracellular volume The kidneys control the composition of electrolytes in the extracellular fluid

Extracellular Electrolytes The extracellular electrolytes are madé up of those in the blood plasma and the interstitial fluids The plasma and interstitial fluids have a similar electrolyte composition, but differ in the content of protein, the latter being greater in favor of the plasma The electrolyte composition of plasma is listed in Table XVI

TABLE XVII

ELECTOLYTE COMPOSITION OF INTERSTITIAL FLUID
(In milliequivalents per liter)

	Base	Acid
Na	145	—
K	3	—
Ca	3	—
Mg	3	—
HCO_3	—	28
Cl	—	111
HPO_4	—	*
SO_4	—	*
Organic Acids	—	*
Protein	—	*

These values omitted to emphasize variations in sodium, chloride and bicarbonate
(Fine J *Care of the Surgical Patient* page 19)

pressure of the entire body, both interstitial fluid and cells, instead of a marked increase in the interstitial fluid alone. This effect could perhaps be achieved more simply by an equal distribution of the sodium chloride itself throughout the two media, but this cannot occur, for it would inflict serious chemical trauma upon the living cells, since normally sodium chloride is not an ingredient of the latter in any appreciable amount

The cell, to retain life and to perform its special functions, must maintain its own inherent chemical pattern, only the environment and the responses to the environment (that is, the functional activity) of the cell can change The interstitial fluid, therefore, which is not a living substance like the cell, but is merely the environment of the latter, bears the brunt of the ionic invasion and protects the cell from change except for a slight rise in osmotic pressure Even this alteration may be said to be nonspecific in character, since it depends on no other chemical change than a moderate loss of water Osmotic adjustments between tissue cells and their environment are made by interchange of fluid rather than of salts

Functions of the Interstitial Fluid The extracellular fluid serves all cells of the body The interstitial fluid is in effect a large homogeneous mass of water and salts which serves as an *osmotic buffer* It guards the cells against the assaults of the external environment It can be moved into the blood stream by the colloid osmotic pressure of the blood or out of it by the hydrostatic pressure, and therefore is *reserve fluid* which can be transported quickly and aggregated wherever it may be needed, for example, in the alimentary canal during digestion Its volume and osmotic pressure may be greatly altered temporarily by the addition or withdrawal of large amounts of salt or water "By means of the lymph stream and the blood circulation the fluid is, as it were, rapidly stirred, meanwhile, so that disturbances of osmotic pressure are distributed over the whole mass of fluid" The cells, protected by their impervious walls, suffer minimal changes of their distinctive chemical composition They may gain or lose a small amount of water by interchange with the interstitial fluid, but the resulting changes of concentration are slight and transitory because they are distributed evenly throughout all the cells of the body by the blood stream, and are soon dispelled by compensatory activity of the secretory organs Potassium and phosphate may escape from the cells under certain conditions

The relatively large quantity of interstitial fluid offers a means of compensation for losses of blood plasma in that such losses are partly replaced by the passage of interstitial fluid into the blood stream Water

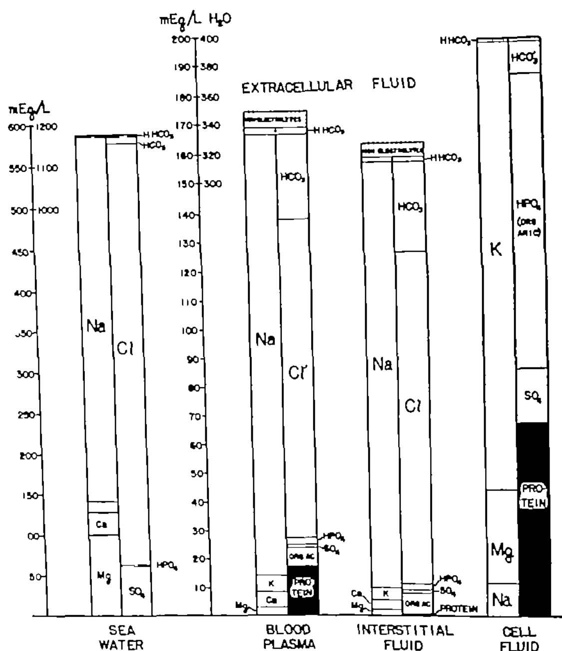


FIG. 26 Chemical Anatomy of Extracellular Fluid. Blood plasma and interstitial fluid and sea water and of cell fluid in terms of acid-base equivalence. (Gamble J L *Chemical Anatomy Physiology and Pathology of Extracellular Fluid* 1939)

tegrates and enters a cell during its growth The chemical composition of intracellular electrolytes is described in Table XVIII

In general differentiated cells contain little or no chloride, and never as much as is present in interstitial fluid Of all tissues examined, muscle contains the smallest amount of chloride. Muscle is able to dispense with chloride because it contains large amounts of protein, phosphate

The concentration of an electrolyte is better expressed in milliequivalents per liter than in milligrams per liter A milliequivalent is a unit of measure of the comparative weights of different compounds, elements, or groups of ions which possess the same chemical value of reaction This unit is determined from the weight in milligrams per liter by use of the following formula.

$$\text{Milliequivalent} = \frac{\text{milligrams per liter}}{\text{atomic weight}} \times \text{valence}$$

Example A solution containing 23 milligrams of sodium per liter would contain 1 milliequivalent of this element because the atomic weight of sodium is 23 and it has a valence of 1

The use of milliequivalents facilitates the expression of the total cations (positive charges) and anions (negative charges) in the body fluids The electrolyte composition of interstitial fluid is shown in Table XVII

A graphic description of chemical constituents of extracellular constituents is seen in Figure 26

The relationship of interstitial volume to changes seen with various surgical conditions has been emphasized and elucidated recently The method of determining changes in interstitial fluid has been by the use of thiocyanate and radiosodium Experiences with these methods indicate wide variation in testing, however, these variations can be partially corrected by the use of these values for estimating the changes in terms of per cent of body weight Cope and Moore studied the redistribution of body water in burned patients and noted a marked increase in the extravascular cellular space

Intracellular Electrolytes and Fluid · The total base concentration of electrolytes in intracellular fluids is about the same as that in the extracellular, but the concentration of the individual basic ions is widely different in the two The chemical composition of fluid within the cells is more complex and variable than that of the surrounding interstitial fluid The cations are made up of large amounts of potassium and magnesium, the anions are the phosphates, sulfates, and protein—the protein having replaced the chlorides of the extracellular fluid

Previously it was thought that the intracellular fluid was free of sodium and chloride, and that the cellular membrane was impermeable to potassium However, recent investigations have changed this concept A small amount of sodium and chloride is found in normal skeletal and cardiac muscles, and this sodium may be withdrawn in certain types of acidosis Potassium leaves a cell when the protoplasm disin-

changes in the volume of body water may cause marked alterations in the amounts of sodium, potassium and chloride eliminated, because of the high concentration of these ions in the body fluids Increased or decreased excretion of certain ions does not necessarily entail any alteration in the concentration of these ions within the body, for the effect upon the body fluids may be offset by the coincident elimination of a corresponding volume of body water Many data have probably been incorrectly interpreted because of failure to consider changes in the total volume of body water

The passage of electrolytes as well as organic substances from intra cellular fluid to extracellular spaces may be linked with cell metabolic activity, which must provide energy for selective transfer of these substances through the cell membrane In marked shifts of the electrolytes between the interstitial and intracellular compartments, it is probable that certain tissues are more capable of executing a more rapid ex change than others The physical and chemical state of intracellular electrolyte and water differ from that of the extracellular No close relationship between transfer of sodium and potassium cations from intracellular to extracellular phases seems to exist. Intracellular potas sium may migrate from within the cell, and yet no change is seen in the intracellular sodium This can occur only in conditions of dehydra tion when the shifted potassium can be carried from the extracellular spaces and excreted by the kidneys Potassium can be increased in the intracellular fluids when it is administered simultaneously with paren teral glucose Water shifts rapidly and readily to and from the cells to balance the increase or decrease in sodium content of the extra cellular fluids

The exchange of electrolytes between the two compartments is not a simple migration by diffusion of the ions across the cell membrane, but rather a result of metabolic activity or actual exchange of energy

The electrolytes in the body fluids are supplied from the external environment except for carbonic acid, which is formed from water and carbon dioxide The latter two are derived from the normal metabolism of the body

WATER BALANCE

The normal, healthy individual automatically takes care of the body needs for fluid Water is consumed in varying amounts by habit and to relieve thirst Water is also supplied by other fluids and food as well as water of oxidation A normal intake is balanced by a normal output through the kidneys, skin lungs and intestines

TABLE XVIII

CHEMICAL COMPOSITION OF INTRACELLULAR ELECTROLYTES
(in milliequivalents per liter)

	Base	*Acid*
Na	20	—
K	150	—
Ca	0	—
Mg	5	—
HCO_3	—	10
Cl	—	70
HPO_4	—	50
SO_4	—	—
Organic Acids	—	—
Protein	—	35

(Fine, J *Care of the Surgical Patient*, page 19)

bicarbonate and at times, lactic acid sufficient to neutralize all the base in the cells Carbonic and lactic acids are normally evolved within the muscle cell itself in consequence of functional activity of the cell Cartilage contains unusually large amounts of sodium

The concentration of the electrolytes of the intracellular fluid varies for each of the individual body tissues, but the general pattern exists throughout

Relation between Extracellular and Intracellular Fluid Gamble, Ross and Tisdall (June, 1923) find that administration of $CaCl_2$ causes no diminution in the concentration of fixed base in the blood serum, yet it induces a greatly increased loss of fixed base in the urine This additional base excreted must, therefore, be derived from the tissue fluids, and the inorganic chemical composition of the latter would necessarily be disturbed *if* the volume of water in the body remained unchanged Actually, there is diuresis, the increased amount of base excreted is derived from a corresponding volume of tissue fluid eliminated at the same time, though this loss of fluid is not manifested by any change in the water content of the blood The extra base in the urine following $CaCl_2$ administration, therefore, is there in consequence of a reduction in the total volume of body water, and does not represent a decrease in the concentration of base within the body

From the data obtained in their study of the action of $CaCl_2$ in the body, these observers conclude that in any study of the metabolism of inorganic substances it is important to consider the possibility of coincident alterations in the total volume of body water Relatively slight

1 Vaporization from the skin and lungs 2 Excretion through the kidneys as urine 3 From the gastrointestinal tract. The water lost through the skin and lungs is called the insensible loss, that lost from the kidneys and gastrointestinal tract, the sensible The amount of water to leave by the three routes is 300 to 600 cubic centimeters via expired air, 300 to 600 cubic centimeters in evaporation from the skin (insensible perspiration), 100 cubic centimeters in the intestinal discharge, and 1200 to 1800 cubic centimeters through excretion by the kidneys

Insensible Loss of Water In a healthy person in a temperate climate, the quantity of fluid eliminated through the skin and lungs is rather constant under normal conditions In an individual not sweating, about two-thirds of the insensible water loss occurs by diffusion through the skin The water loss through the respiratory tract depends on the volume of respiratory exchange and content of water of the inhaled and exhaled air These two, in turn, are dependent upon the temperature and humidity of environmental air, since exhaled air is 88 per cent saturated with water at 33 degrees Centigrade Water loss from lungs is hard to estimate in the presence of hyperpnoea. Water loss from lungs is not associated with electrolyte loss

The insensible loss of water from the skin is dependent upon a gradient diffusion through the skin This is based upon the skin temperature if the surface is dry Little electrolyte is lost with this insensible fluid

In response to an increased need for dissipation of body heat, the sweat glands function and fluid is elaborated upon the surface of the body The volume of sweat elaborated is in amounts equal to that required to maintain body temperature when the metabolic production of the heat and the positive heat balance from the environment are greater than the losses produced by evaporation of the insensible water and by the heat losses through radiation, conduction and convection Up to 100 per cent of the body heat may be eliminated by sweat Prolonged, profuse sweating produces great losses of fluid and electrolytes At high environmental temperatures men at hard work may lose as much as 2 5 liters per hour The quantity of electrolytes in sweat is highly variable and at times unpredictable Approximate estimates for salt content of sweat are 0.2 per cent potassium chloride, or 25 to 50 millimoles per liter Sweat contains 15 millimoles of potassium

Water Reserves in Skin and Muscles After hemorrhage, the fluid which enters the blood from the tissues causing the blood to become diluted is derived largely from the skin, for on analysis of the various

Body Fluid and Physiologic Role of Water: Approximately 70 per cent of the body weight is water This water is in the intracellular and extracellular compartments The intracellular water constitutes 50 per cent of the body weight, whereas the extracellular equals about 20 per cent of the body weight In a 70 kilogram man, the intracellular volume is equal to 35 liters of fluid and the extracellular about 14 liters The extracellular is made up of two compartments—blood plasma, 5 per cent of body weight or about 5 liters, the interstitial which includes the lymph and lies between the vascular compartment and the tissue cells This is equivalent to 15 per cent of the body weight, or 11 liters

The water may move about from one compartment to another without restraint This fluid exchange between compartments is in a dynamic state The large quantity of interstitial fluid affords a means of compensating for losses of blood plasma Water intake is applied almost entirely to the maintenance of extracellular water volume The intracellular fluid volume is derived from the water obtained by the oxidation of food substances The distribution and partition of fluid into the various reservoirs is associated with a combination of mechanisms involving the circulation of the blood, the level of plasma protein, semipermeability of capillary and cell walls, selective permeability, and rate of solubility and diffusion of cations and anions

Sources of Body Water Water is supplied to the body as 1 Water or fluid we drink 2 Water contained and derived from food 3 Water of oxidation The water of oxidation does not always correspond directly to the food ingested, for in starvation, 300 to 500 cubic centimeters of water becomes available from the water of oxidation of body substances burned for energy The amount of water oxidation depends upon the character of the foodstuff burned and the end product of oxidation It is highest for fats—combustion of 1 gram of fat yields approximately 1 gram of water, 1 gram of carbohydrate yields about 0 6 grams of water, and 1 gram of protein about 0 4 grams of water In an ordinary diet, the so-called solid foods contain as much as a liter of water per day in physical and chemical combinations About 300 to 500 grams of water per day are derived from the oxidation of organic food materials on the usual mixed diet—that is, about 12 grams of water for each 100 calories

In temperate climates the average adult receives approximately 2500 cubic centimeters of water per day—1200 cubic centimeters from liquids taken orally, 1000 cubic centimeters from water in solid food and 300 cubic centimeters as water of oxidation

Water Loss: Water is removed from the body by three routes

require about 250 cubic centimeters of water for excretion in urine which is maximally concentrated

In the presence of renal disease and a fixed urine specific gravity, the amount of water required for urine formation is designated by the volume which will contain the substances to be excreted The amount of water needed to excrete the 35 grams of urinary waste material at varied specific gravities is shown in Table XIX A total water intake of 150 cubic centimeters per 100 calories metabolized is required to produce the 85 cubic centimeters of urine at specific gravity of 1 012 Four liters are necessary in an average individual

TABLE XIX

MINIMUM AMOUNT OF WATER NEEDED BY KIDNEYS TO EXCRETE 35 GRAMS OF WASTE MATERIALS

Condition of Kidneys as Shown by Maximum Concentrating Ability	*Sp Gr Urine*	*Water needed cc*
Normal	1 032–1 029	473
Diseased*	1 028–1 025	595
	1 024–1 020	605
	1 019–1 015	850
	1 014–1 010	1439

* Chronic nephritis, pyelonephritis, renal tuberculosis etc.
(Maddock, W G *Am J Surg 46* Compiled from data furnished by Lashmet F H. and Newburgh, L H. *J Clin. Investigation 11*)

Sensible loss of fluid through the gastrointestinal tract is usually limited to 100 cubic centimeters This is true if the 8200 cubic centimeters of fluid excreted into the intestinal tract is reabsorbed When the intestinal fluid is lost at an abnormal rate, dehydration will occur rapidly and will be accompanied by disturbances in electrolyte balance.

Addition or subtraction of a small amount of sodium chloride changes the boiling point, freezing point, solvent power, electrical conductivity and many other properties of solutions Therefore, it is not surprising that changes in sodium chloride concentrations in the body have profound effects,

Sodium is the chief component of the basic ions of the extracellular fluid Its concentration is controlled by its reabsorption from the glomerular filtrate as it passes down the renal tubules The kidney therefore plays a dominant role in regulation of isotonicity of extra cellular fluid. When sodium is retained, the volume of extracellular fluid must increase if osmotic equilibrium is to be maintained When sodium is lost, the volume decreases,

tissues, only the skin shows loss of a significant amount of water The skin has normally a high chloride content, and this is further indication that the skin contributes the major part of the fluid for restoration of blood volume in hemorrhage, for the total solids of the blood decrease in concentration, whereas the chlorides increase by 20 per cent or more As a result of deprivation of food and water, the water content of most of the tissues decreases In the rabbit the decrease has been found to be greatest in the skin (4 per cent), muscles (4 per cent) and lungs (2 per cent) These figures indicate that the available water reserves of the body are stored mainly in the skin and muscles This does not necessarily mean that the tissues which release the most water to the blood in time of need are the ones with the highest water content The degree to which the various tissues give up water in anhydremia bears no relation to the richness of their water content The skin is relatively poor in water, yet may lose a considerable part (one-fifth) of its water in case of need, the intestines and spleen are rich in water, yet they lose little of it

Water never moves about alone in the body, but always carries salt with it, and vice versa Nevertheless there is no definite relation between the chloride distribution and the water distribution in the body The blood and skin, for example, exceed all other tissues in chloride, yet they have a relatively low water content

Sensible Loss of Water The relatively constant loss of fluid through the skin and lungs has a "preferential right" over the available fluid The remaining fluid is all that is available to the kidney in which to excrete the waste products and for that 100 cubic centimeters which will be lost through the gastrointestinal tract The sensible loss through the kidneys in a healthy person varies between 1200 and 1800 cubic centimeters The kidney is responsible for removing any excess fluid within the body When the renal tubules are able to concentrate urine normally, a minimum of 500 cubic centimeters of urine must be excreted to provide sufficient fluid to carry the daily solids (35 grams) It is the kidney which is most closely associated with maintenance of composition and volume of body fluids Not only does the kidney eliminate extra amounts of normal constituents of body fluids, but it also eliminates abnormal metabolic waste products Another function of the kidney is conservation by reabsorption from the glomerular filtrate of essential components of the body fluids and chemicals, such as water, sodium and glucose These substances may filter through the glomeruli in large quantities Abnormal large renal loads are produced by ketosis, and glycosuria Fifty grams of dextrose or 9 grams of sodium chloride

Water Loss at Operation Coller and Maddock (1932), in a study made to determine the degree of dehydration directly attendant upon surgical operations, measured the loss of body fluid occurring during operation and the first four hours after operation They found that under ordinary conditions the total loss during the entire period averaged about 1 liter.

Fuge and Hogg found that the average insensible loss of water in 12 surgical patients was 1457 grams per day, and constituted 39 4 per cent of the total fluid output. The amount of insensible loss was not affected by the type of operation, nor was it decreased in the presence of dehydration White *et al*, report an average loss of 200 to 1000 cubic centimeters of water (including sensible loss) by evaporation from the skin and lungs during extensive craniotomy The coincident loss of blood was from 500 to 1500 cubic centimeters and both losses must be considered in estimating replacement needs The authors state that a slightly dehydrated state postoperatively is desirable in order to prevent edema of the brain

Infants require much more water per pound of body weight than adults, according to Myers, who states that the loss of 10 per cent of the body water has grave effects Because the proportion of blood to body weight in a child is 1 20 as compared to 1 13 in an adult hemorrhage is poorly borne and surgical shock is easily produced The narrower margin of safety in surgery in infants and children necessitates special attention and preparation

In addition to the water lost at operations by vaporization and increased visible sweating, one must consider the loss of blood Moderate losses in blood volume are compensated for by shifting of interstitial fluid to the vascular system Blood lost at operation is frequently not recognized or is minimized The following figures from Coller, Crook and Iob relate the average blood loss in surgical operations

	Per Cent
Radical mastectomy—average of 821 cubic centimeters	17 /
Hemithyroidectomy and subtotal thyroidectomy—average of 3/9 cubic centimeters	11 /
Secondary and plastic operation on the biliary tract—average of 594 cubic centimeters	14 6
Combined abdominoperineal resection—average of 410 cubic centimeters	9 5
Complicated gastric lesions—average of 599 cubic centimeters	13 6

Water Loss After Operation Negative fluid balance exists in most patients after surgery because they have taken in little by mouth, and

Disposal of Injected Salt Solutions: After intravenous injection of saline solution the increase in water content of the tissues is greatest in the case of the muscles, skin and kidneys, according to Rowntree Since the muscles comprise such a large part of the body (about 40 per cent of the body weight), they take up the greatest part of the added water (more than two-thirds) Massive infusions of one per cent sodium chloride are well tolerated in animals and man. Cutting *et al*, from animal experiments, estimate that the lethal volume for an average sized man, given at the rate of 350 cubic centimeters per minute, is about 35 liters However, based on findings in the cat, this figure is of doubtful accuracy for man Hypertonic solutions are lethal at smaller amounts and at slower rates These observers state that the cerebrum is the only organ which does not store water, and that cerebral edema definitely does not occur after massive infusions of one per cent solution of sodium chloride

Fluid Requirements of Surgical Patients. Valuable contributions regarding the water requirements of surgical patients have been made by Coller and Maddock (1933), as a result of accurate observations in clinical cases They found that the insensible loss of water (from lungs and skin) in the seriously ill surgical patient amounts to about 2 liters per day In the presence of fever or hyperthyroidism the amount may be as much as 3000 cubic centimeters This water lost insensibly, being essential to the maintenance of normal body temperature, has "preferential rights" over the water required for urine formation, for the kidney has to function with whatever water is available after all other water-using physiological processes have been provided for

The water requirements of the surgical patient can be determined by adding to this factor of 2 liters of insensible loss any losses from the gastrointestinal tract, any loss from sensible sweating, and an amount of water necessary for the required volume of urine

Fantus states that the 24-hour quantity of urine should be as regularly recorded in critically ill patients as the pulse rate and temperature He calls attention to the fact that for the maintenance of life, water is second only to oxygen in importance, and is more urgently necessary for life than food He stresses the danger of any delay in meeting fluid requirements because irreversible tissue changes due to dehydration may occur which an infusion given 24-hours too late may be incapable of relieving Thirst is a fairly sensitive index of hypohydration in the normal individual but is unreliable in sickness except that when present it always calls for relief measures Semiconscious or unconscious patients often are not given enough water

water deficits are proportional to the ratio of extracellular to intra cellular water The kidney will excrete potassium in preference to sodium or urea in instances of water starvation If potassium deficits are associated with alkalosis, this alkalosis is refractory to sodium chloride therapy when the potassium deficits persist.

Recent studies in postoperative patients by a group at the University of Michigan showed a high initial rate of both water and potassium excretion in the urine when infusions of saline or glucose in water were given The potassium excretion far exceeded 2 7 milliequivalents per gram of nitrogen loss, which is expected as part of normal catabolism, The greater the extent of operative procedure, the greater the loss of potassium, this loss always exceeds the expected nitrogen output by a wide margin It is suggested by Darrow that potassium deficits occur when output exceeds intake, with changes in equilibrium as in alkalosis, during rapid storage of nitrogen and under action of adrenal cortical hormone The finding, in patients, of a low chloride, low potassium and a high bicarbonate is rather good proof for potassium deficits In surgical patients potassium losses through the gastrointestinal tract, from suction or fistulae or diarrhea, may be considerable and are not infrequently associated with losses of sodium. The administration of parenteral fluids to patients undergoing minor surgical procedures will cause an increased loss of potassium.

Potassium deficits from excessive postoperative loss are best detected by drop in the plasma potassium levels It might be well to add at this point that these recent advances in the changes in potassium after surgery are only possible because of the development of a flame photometer This instrument makes possible the rapid and numerous determinations of sodium and potassium with accuracy

Symptoms of potassium deficiency appear when levels of 3 0 milliequivalents are approached and more severe expressions are found with potassium levels of 2 6 milliequivalents per liter, or less Two groups of symptoms are noted with potassium deficiency The first is the acute syndrome of skeletal muscle weakness, sometimes with paralysis of the intercostals and diaphragm, as is described in diabetic acidosis with dehydration or in chronic nephritis The more common types of symptoms are those of the second group, which usually appear from the fourth to the ninth postoperative day These symptoms are drowsiness languor, persistent ileus with moderate distension, anorexia and weakness, accompanied by some peripheral edema, oliguria and hemoconcentration Not all symptoms are present in any one case and clinical patterns are varied.

The electrocardiographic changes found with hypokaliemia have

are constantly losing fluids through vomiting, increased insensible loss from fever and sweating, and from the abnormal losses from the gastrointestinal tract by suction These abnormal losses from the gastrointestinal tract may be seen when secretions are wasted through fistulae and biliary drainage. Recent work by Coller, Cooper and others on the depressed renal function seen after serious operations, makes one limit the amount of fluid given immediately after surgery These authors find that renal function is usually depressed during the first 12 to 48 hours after a serious operation, and selective excretion of electrolytes is temporarily disturbed This is reflected in the retention of sodium chloride and water within the extracellular spaces. This same impaired function is seen with the parenteral use of glucose In the early postoperative period low urinary output is the rule, the extent of oliguria being in direct proportion to the severity of the operative measures, and not related to the volume of fluid administered These same authors advise the limitation of fluids on the day of surgery to the blood required to replace that lost and a volume of 5 per cent dextrose in water sufficient to replace the insensible water loss

Potassium Loss After Surgery Potassium is the major cation of the body and exceeds sodium by a ratio of more than two to one Potassium plays an important role in the physiology of a normal subject and is particularly important in the postoperative patient maintained on parenteral feedings Benedict reported a 2 87 millimeter loss of potassium with each gram of nitrogen in the second to eleventh day after starvation Butler described large losses of potassium in the stools and urine of infants with diarrhea Darrow suggested and described a very large loss of potassium in the stools and urine of infants with congenital alkalosis and diarrhea This excessive loss of potassium is often found with extracellular dehydration wherein there is a loss of sodium by shifts of sodium and water into the cells The replacement of extracellular fluid with saline or saline-bicarbonate mixtures restores extracellular defects but increases the potassium loss because additional sodium enters the cells. In studying the effect of dehydration on various fluid compartments and electrolyte shifts, Elkinton and Winkler observed that 20 to 38 per cent of intracellular water could be lost while from 30 to 50 per cent of the intracellular water was mobilized, and that potassium loss was much greater than could be explained simply by tissue catabolism. Further study, by these authors, in human subjects revealed a predominance of extracellular water losses in water deprivation, during the early stages, whereas later the losses were predominantly intracellular and potassium loss far exceeded that expected from catabolism alone In four days of water deprivation, the

first few grams of KCl over a period of one to four hours, this usually takes care of the emergency phase of potassium depletion From then on replacement may be less rapid, and indeed leisurely, care being taken to continue therapy (2 to 4 Gm of KCl per day) intravenously *above* daily losses Once plasma bicarbonate content has fallen to normal levels after alkalosis, one can usually conclude 'the potassium situation is well in hand'"

Measurement of Blood Hydration For estimating the state of hydration of seriously ill surgical patients, Drew *et al* recommended the use of the following four tests 1 Hematocrit determination of the proportion of cells to plasma in venous blood 2 The specific gravity of the blood 3 The specific gravity of the plasma 4 The protein concentration of the plasma as *calculated* from the specific gravity of the plasma

These tests, which are quite accurate and easy to perform are of most value when used in conjunction with one another and when repeated determinations are made in a given case The normal values are as follows

Hematocrit Males—46 per cent cells, range 42 to 50 per cent
Females—41 per cent cells range 39 to 43 per cent
Blood specific gravity Males—1 0566 daily range 0 0033
Females—1 0533 daily range 0 0033
Plasma specific gravity 1 0270 daily range 0 0033
Plasma protein 7 0 grams per 100 cubic centimeters range 5 9 to 7 9 grams per 100 cubic centimeters

To the above listed tests may be added plasma carbon dioxide combining power, as a means of estimating alkalosis and acidosis Measurements of blood hydration without determining the acid base and electrolyte values does not give a truly accurate evaluation of hydration, changes in electrolytes and the presence or absence of the varied types of dehydration

In the control of fluid balance, laboratory determinations mean little unless they are considered in relation to the patient's history and physical findings A record of daily normal losses, abnormal fluid losses, vomiting or gastric drainage, biliary drainage, and serous ooze are an integral part of the clinical evaluation of hydration One cannot underestimate the importance of accurate measurements of intake and output, especially the urine volume In measuring the urine volume one should add urine specific gravity, pH, and sodium content by the simple silver chloride method *These are helpful in estimating electrolyte needs as well as the state of hydration*

received considerable study and description They are slightly prolonged Q-T interval, decreased height and inversion of the T wave, rounded and prolonged T waves, depression of the S-T segment, and possible inversion of the P waves, extrasystoles and auriculoventricular block The electrocardiographic changes correlate only approximately the decrease in serum potassium

Snyder and Snyder studied serum potassium levels and urinary excretion rates of water and potassium in 100 surgical patients These authors feel that knowledge of the serum potassium in the management of complicated surgical cases is necessary They also say that "in the 38 consecutive major cases, serum potassium levels less than 3 8 milliequivalents per liter were found in 26 cases Potassium therapy was deemed essential in 7 of these"

A good part of more recent knowledge of potassium deficiency in surgical patients has been presented by the able work of Everett Idris Evans He advises strong and close attention to any case of "uncorrected alkalosis after adequate water and sodium chloride therapy" and suspicion of "potassium deficiency if this abnormally exists" Evans states that the two most important matters in treating a patient for potassium deficiency are (1) the severity of the deficiency, and whether replacement must be rapid or may be slow, and (2) the ionic composition of the replacement fluids Various solutions are suggested Darrow advises 0 26 grams of potassium chloride per kilogram over a period of four to eight hours Lockwood uses two separate solutions, 2 33 grams of potassium chloride plus 6 44 grams of sodium chloride per liter, and 2 33 grams of potassium chloride in one liter 5 per cent glucose in water

The treatment of potassium deficiency as given by Evans is as follows "The emergency treatment of severe potassium deficiency requires considerable care and a nicety of clinical and chemical judgment, because the patient's condition (extreme muscular weakness, etc) may demand the relatively rapid infusion of large amounts of potassium chloride in a one- to two-hour period If the state of renal function is not known, potassium chloride infusions should be preceded by the intravenous infusion of 600 to 800 cubic centimeters of 5 per cent glucose in water to stimulate urine flow A pretreatment estimation of plasma potassium is helpful, and if the potassium level is low (below 3 0 MEQ), relatively rapid rates of potassium administration are less hazardous Serial electrocardiograms before and during potassium administration may be used to guide rapid potassium therapy (see Bellet) Our experience indicates that the important thing is to give the

simultaneously with the hematocrit, one can measure hemoconcentration. Serial hematocrit values made at frequent intervals show the total amount of fluid required by the patient. This is only true if there are no changes in red cell count and total protein from other causes. Thus, if an individual is losing blood, serial hematocrits are of little value in determining hydration, but of great importance in recognizing hemorrhage. Also, in the face of nutritional deficiency and hypoproteinemia, serial total proteins offer little unless we know the amount of protein present before starting the serial determinations. Characteristic findings by means of the aforementioned tests in some clinical conditions of surgical interest are as follows. *Dehydration*. The values are above normal in all four tests. *Shock (unaccompanied by hemorrhage)*. The values are above normal in all four tests. *Hemorrhage*. There is an immediate decrease in the hematocrit value (cell volume) and in the specific gravity of the whole blood, little or no decrease in the specific gravity of the plasma or in the plasma protein concentration (because of quick readjustments of plasma proteins and of circulating blood volume). *Combined loss of fluid and protein* (as in severe burns, infections with copious purulent exudates, especially in serous cavities). The hematocrit value and the specific gravity of the whole blood are increased, the specific gravity of the plasma and the plasma protein concentration are decreased. *Impending edema*. There is a progressive decrease in the plasma specific gravity and plasma protein concentration.

Recent investigations with blood volume tests with use of a dye and thiocyanate determinations of extracellular fluid volume add to our understanding of changes related to hydration. These tests may be performed as part of the laboratory procedures used to accurately calculate hydration.

From a purely clinical standpoint, hydration is best measured by an accurate estimate of total intake, and total loss. The daily weighing of patients as suggested by Wangensteen and his group is an adjunct method of evaluating daily fluid needs, fluid balance or the degree of hydration.

SALT BALANCE

In a discussion of salt balance in surgical patients Bartlett *et al.* give as the two chief functions of sodium chloride in the body, (1) the regulation of acid base balance and (2) the control of the amount and distribution of body water, the latter function being effected through the influence which the salt has on osmotic pressure. The following features of salt metabolism are stressed by these authors with reference to

Specific Gravity of the Blood and Plasma: The emphasis now placed on measurements of the specific gravity of the blood and of the plasma is a consequence of the development by Barbour and Hamilton of the *falling drop* method of determining the specific gravity of any fluid This very accurate method is based on the fact that the time required for a drop of a given volume to fall a fixed distance through a fluid with which the drop is immiscible depends, aside from temperature and other controllable factors, upon the specific gravity of the drop From a graduated pipette a drop of blood or plasma of known size is released into a vertical tube containing a mixture of bromobenzene and xylene and its fall between the two marks on the tube is timed with a stop watch The same process is carried out with a standard, that is, a solution of known specific gravity, and the specific gravity of the blood or plasma is then calculated, a correction being made for temperature

Plasma Protein Determination: The hematocrit value (cell volume percentage) and the specific gravity of the whole blood vary in the same direction as the hemoglobin concentration and red cell count of the blood The red cells, because of their greater weight, are of more influence on the specific gravity of the whole blood than are the plasma proteins Therefore the concentration of the plasma proteins cannot be calculated from the specific gravity of the whole blood, but only from the specific gravity of the *plasma*, there is a constant relationship between the specific gravity of plasma and the protein concentration For each increase of protein of 1 gram per 100 cubic centimeters the specific gravity rises 1/340, in other words, each increase in specific gravity of 0 0001 signifies an increase in plasma protein of 0 13 grams per 100 cubic centimeters The determination of the plasma specific gravity in general has more clinical value than that of the whole blood specific gravity, because the former affords knowledge also of the plasma protein value Drew *et al* employ the formula P = 340 1 (G—1 00687) ± 0 103 in which P represents grams of protein per 100 cubic centimeters of plasma, G represents the specific gravity of the plasma and 1 00687 signifies that portion of the specific gravity of the plasma produced by the components of the plasma other than the proteins These authors found this formula inapplicable in cases of marked lipemia, hypercholesterolemia, severe diabetes, excessive bilirubinemia and gross hemolysis

Interpretation of Laboratory Tests Abnormal changes in hydration of the body are usually reflected by alterations in specific gravity of whole blood or plasma If plasma protein levels are determined

that the body fluids may not become hypotonic. The retained nitrogen cannot be washed out with water, it must be driven out with salt.

Plasma Chloride Level in Salt Depletion In salt depletion, the critical level of plasma chloride at which symptoms appear varies greatly in different individuals, especially since the first symptoms are subjective, such as weakness, lassitude, drowsiness, dulling of the sense of taste, loss of appetite, nausea. Symptoms may or may not be present when the plasma sodium chloride has fallen to 500 milligrams, but at 450 milligrams nearly all patients will have symptoms If the treatment of hypochloremia is to be governed by plasma chloride determinations one must allow 12 hours after the salt administration in order to get a true reading On the average, about 20 grams of salt is needed to raise the plasma chloride 100 milligrams in hypochloremia, according to Bartlett *et al* These authors find the plasma chloride level a satisfactory index of the chloride concentration of the whole body, if, for example, it is 20 per cent below normal, they assume that 20 per cent of the body chloride has been lost This is true, of course, only in case there is no coincident marked deficit or excess of body water They recommend the simple rule of giving 0 5 grams of salt per kilogram of body weight for each 100 milligrams deficiency of plasma chloride concentration A still simpler procedure which obviates plasma chloride determinations, is the employment of urinary chloride determinations As long as there is more than 1 gram of salt per day in the urine there is little danger of serious salt depletion

Maddock and Coller emphasize the role of salt in the causation of generalized edema, two chief factors in the production of edema being hypoproteinemia and excess of salt In sickness the amount of salt which can be excreted by the body is much lower than in health, due to such factors as malnutrition sepsis, hemorrhage, wound drainage, anesthesia and liver and kidney disturbances—all of which cause a tendency toward retention of salt The result of salt retention is hydremia rather than hyperchloremia Hence the blood sodium chloride concentration is no index of excessive salt retention In most cases in spite of the presence of edema, the blood chloride values are within the normal range, and sometimes there is a definite hypochloremia

These authors stress this "paradox of low blood electrolytes with edema," which causes some embarrassment in the treatment of cases of abnormal losses of salt according to the "clinical rule" which they have advised This rule is that for each 100 milligrams of plasma chloride deficit per 100 cubic centimeters of plasma, 0.5 gram [illegible]

surgery Whereas chloride can be replaced, if need be, by the bicarbonate ion, sodium cannot be replaced by any ion and its loss is necessarily attended by dehydration The normal concentration of sodium chloride in the *plasma* is from 560 to 630 milligrams per 100 cubic centimeters (450 milligrams per 100 cubic centimeters *whole blood*) From the plasma sodium chloride concentration in milligrams per cent, one can calculate the plasma chloride ion concentration in milliequivalents per liter by dividing the plasma sodium chloride value by the factor 5 85 The normal plasma chloride value is 96 to 103 milliequivalents per liter (m Eq /L)

The amount of sodium chloride contained in the entire body is about 150 grams The normal daily intake is from 3 to 12 grams, nearly all of this amount is excreted in the urine, the bowel and the skin eliminating about one-fourth gram each The sodium chloride intake is obtained from food (1 to 2 grams per day) and from salt added to food as taste demands A healthy normal individual may handle as much as 35 to 40 grams of sodium chloride because the kidneys are able to excrete salt in the urine in concentrations up to 2 per cent

An excessive intake of salt is well tolerated in health, being easily offset by increased excretion In ill health, however, any excess salt taken in is likely to be retained to some extent, causing edema, and for some unknown reason the plasma chloride concentration may remain low in spite of such excessive administration of salt. An excessive output of salt can occur through vomiting, diarrhea, excessive perspiration, intestinal, biliary or pancreatic fistulae, serous discharges or wound exudation The average salt concentration in the fluids thus lost is about the same as that of blood plasma, namely, 5 to 6 grams per liter, or less The salt abnormally lost in this way may be in hypotonic but never hypertonic solution, therefore, replacement never calls for hypertonic solutions A lowered plasma chloride concentration indicates a lowered salt concentration in the other body fluids and tissues, but the plasma chloride is not a wholly adequate measure of salt depletion.

A salt poor diet causes no marked change in plasma chloride, whereas the loss of gastric or intestinal secretions causes a prompt fall When, in excessive salt loss, there is loss of equal amounts of sodium and of chlorine, the acid-base balance of the body suffers no disturbance, but body water is depleted, with the result that nitrogen elimination may be inadequate Even if water is given freely, it does not remove the nitrogen retention, for it seems that urea is purposely retained by the body in an effort to replace the missing salt with some substitute, in order

that the body fluids may not become hypotonic. The retained nitrogen cannot be washed out with water, it must be driven out with salt.

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substance administered in a given time, over and beyond the amount excreted

In one of the studies on postoperative salt intolerance, Coller *et al* found that the injection of isotonic sodium chloride solutions within a 30-hour period, after combined abdominal perineal resection, is attended by a retention of 53 per cent of the sodium, 46 per cent of the chloride, and 19 per cent of the water This retention of salt requires a withdrawal of 2 liters of fluid from the intracellular compartments to maintain isotonicity If hypotonic salt is given to these patients, a greater amount of water is available for excretory function of the skin and lungs, and the intracellular compartment is not involved The human kidney, after surgery, does not elect to guard a physiologic saline solution The indiscriminate infusion of normal saline solution in water or in 5 per cent glucose after surgery may be followed by a relative deficit of water, the retention of salt solution in the body, and/or a deficiency of potassium A retention of salt produces changes in the composition and volume of the body fluids

It is advised that on the day of operation no salt be given and the fluid injected be only that amount required to balance insensible loss After the first 48 hours following surgery, renal function begins to regain some of its normal physiologic function and salt may be given It is better to err on the side of little salt rather than too much The use of daily maintenance doses of salt after surgery is of questionable value

Another danger of excessive postoperative administration of salt is its effect on potassium loss The greater the sodium retention, the greater the potassium loss Hence, alkalosis and hypokalcemia can develop readily in patients treated with gastric suction and parenteral saline

Chloride Balance in Gastric and Duodenal Suction Drainage In a study of the fluid and sodium chloride balance in patients treated with continuous gastric and duodenal suction, Paine and Armstrong found that administration of 2000 cubic centimeters of normal saline daily suffices to maintain a positive chloride balance and to prevent any serious alkalosis Even when less is given, it is four or five days before any harm from dechloridation develops, as revealed by alkalosis, decrease of blood chloride and increase of blood nonprotein nitrogen It was found that urine chloride was as good an index as plasma chloride and that there was no danger of achlorhydric alkalosis if the kidneys excreted 3 grams of chloride per day In many cases, despite the giving of 3000 cubic centimeters of 5 per cent glucose with the production of glycosuria acetone and diacetic acid appeared in the urine

Disturbances in Sodium Concentration An excellent summary of

sodium chloride per kilogram of body weight should be given Maddock and Coller observed that this rule worked well in acute cases in which the loss of salt had occurred recently, the blood chloride level returning promptly to normal under this treatment In chronic cases, however, and in severer cases, the blood chloride failed to reach normal, and the patients gained in weight under treatment according to this rule They ascribe this to low blood proteins and other secondary disturbances present in the severer and more chronic cases Though they state that "the surgical staff may well feel guilty when some patients come to autopsy with waterlogged tissues," it is impossible for one to determine just how much to modify their clinical rule in applying it to each patient This rule is incompatible with the clinical fact of "the paradox of low blood electrolytes with edema"

They agree that in shock and in burns, the sodium chloride lack is associated with a deficit of plasma, hence there is need of whole blood or of plasma, plus only a moderate amount of saline solution

In this connection it should be remembered that salt solution normally comes into and goes out from the body and all of its compartments every day, whereas the plasma remains fixed in location and in amount, and exerts a regulatory influence over the movement of the salt solution The sodium chloride solution may be compared to the currency in circulation and the plasma to the banking system One cannot expect to remedy any serious plasma defect by even the most strenuous administration of sodium chloride solution Hence, in burns, salt should be given sparingly, especially in the later stages when there may be hypoproteinemia and sepsis, hypochloremia may persist and be unsuitable as a guide for treatment

Postoperative Salt Intolerance Many authors have focused attention on the potential danger of large amounts of physiologic saline in postoperative patients It was Trout and Evans, who, over 30 years ago, cautioned against the excessive use of saline solutions

After surgery, there is a transient renal irritation which impairs kidney function This impaired function lasts for three to seven days If additional amounts of sodium are administered postoperatively, they are not excreted but are retained within the extracellular spaces, and a portion shifts into the cells With this salt retention, there is translocation of fluid in the body—an increase in extracellular volume and to some degree this increases the intracellular fluid Any substance injected into the body must be excreted by normal or abnormal kidneys The rate of excretion of a substance is practically directly related to the load. The load is described as the total cumulative excess of a

10 Severe burns—extreme fluid loss of both plasma and electrolytes The plasma deficiency should be corrected first, then, that of water and salt. Plasma and saline solution are indicated

Dehydration The clinical manifestations of dehydration appear when there is a fluid depletion corresponding to 6 per cent of the body weight.

When dehydration is present, there is a history of weight loss, abnormal losses by urine, stool, vomiting, insensible sweating and other routes Physical examination reveals the presence of weight loss, sunken facial expressions, dry, hot skin, dryness of the buccal mucosa and tongue, loss of skin turgor, fecal masses in the bowel, a subjective thirst, elevated temperature and pulse rate, muscular hypertonicity, hyperactive reflexes, positive Chvostek or Trousseau sign or carpopedal spasm and in infants a retraction of the fontanels

The laboratory changes have been partially outlined in the section

TABLE XX

DISTURBANCES IN FLUID EQUILIBRIUM

Water Disturbances	*Extracellular Salt Water Disturbances*
1 Volume. a. Deficit. (The water content of the body in relation to total solids is diminished) 1 Acute. 2 Chronic b Excess 1 Absolute. (The water content of the body in relation to total solids is increased.) 2 Relative. (The water content of the body is increased in relation to the mobile sodium content The actual water content of the body in relation to total solids may be in excess *normal or in deficit.*)	1 Volume. (Changes in relation of extracellular salt water volume, base content of body to total body solids.) a. Deficit. (Base deficit * sodium deficit.) b Excess. (Base excess,* sodium excess.) 2 Composition. (Departure from the electrolytic pattern of "normal" extracellular fluid) a. Acidosis. Alkali deficit * bicarbonate deficit.) b. Alkalosis (Alkali excess * bicarbonate excess.) 3 Distribution. (Reciprocal variations in the extracellular salt water volume of various tissues with the total extracellular salt water volume remaining constant—e g., other tissues lose extracellular salt water to the skin when it is injured.†)

* Peters and VanSlyke.

† Reciprocal variations in the volume of distribution of sodium in relation to the solids of various tissues.

(Moyer C *Surg., Gynec. & Obst., 84*)

disturbances which may occur in sodium concentration is found in *Care of the Surgical Patient* by Jacob Fine The following conditions according to Fine may produce disturbances in sodium concentration:

1 Pyloric obstruction—loss of chloride (anion) is in excess of sodium (cation) Therefore, the bicarbonate rises to restore the chloride loss, and causes an alkalosis Following this, dehydration ensues because sodium is excreted along with water in order to equalize the acid-base balance Physiologic saline, not water alone, is necessary to correct the imbalance

2 Pancreatic fistulae—loss of sodium is in excess of chloride Since water is also lost, there develops a state of dehydration, with the resultant acidosis

3 Diarrhea—loss of whole gastrointestinal juice and loss of sodium in excess of chloride with resultant acidosis In prolonged diarrhea, acidosis and dehydration develop

4 Use of acid-producing salts for the treatment of edema—depletes the base necessary for elimination of the acid and water is lost with the base

5 Excessive sweating—produces excessive loss of salt and water Oral administration of one-half per cent sodium chloride remedies this type of imbalance

6 Acute Addison's disease—loss of sodium excessive because renal tubules do not reabsorb the sodium Administration of salt solution is the treatment of choice for the acute symptoms and manifestations

7 Ingestion of hypertonic saline solutions—causes a rise in interstitial sodium in patients with some degree of dehydration The excess is too great to be removed by the functioning normal kidney, for the kidney can only excrete salt up to 300 milliequivalents per liter of urine Balance can only be restored by water

8 Edema—due to retention of sodium and water, usually in the presence of some degree of protein deficiency, as is seen in hypoproteinemia A low salt intake is recommended so as to dilute the interstitial sodium concentration, because the kidney is able to excrete this along with the fluid of edema This edema is seen in the skin, subcutaneous tissues, the lungs, or at the injury sites

9 Traumatic shock—caused by local injury with accumulation of blood, plasma, or interstitial fluid at site of injury and perhaps at other areas This extravasated fluid comes from the interstitial spaces and contains large amounts of water and sodium The cellular potassium moves into the interstitial spaces If hematocrit levels are elevated because dehydration is present, water, blood or plasma, are required Hemorrhagic shock usually produces only slight dehydration

medical shock and responds best to blood, plasma and electrolytes Moyer describes well the disturbances in fluid equilibrium Tables XX and XXI are from his reference.

FLUID THERAPY FOR ELECTROLYTE AND FLUID IMBALANCE

As far as is possible, therapy should be based on an estimation of changes in tissue composition, and the rate of water and electrolyte losses as well as daily requirements and expenditures Some of the principles involved in planning fluid therapy are 1 Supplying the volume of fluid needed for daily expenditure—about 3500 cubic centimeters, that is, 2000 cubic centimeters which are lost by vaporization from the lungs and skin, plus 1500 cubic centimeters which are eliminated as urine 2 Supplying the electrolytes required for daily consumption and replacing the electrolyte deficit after estimation with solutions which provide sodium, potassium, chloride and phosphate 3 Supplying calories and nutrition to varied abnormal metabolic reactions or to overcome such reactions as seen in diabetes, adrenal insufficiency, *renal failure, diarrhea and continuous gastric lavage and* suction 4 Supplying blood or plasma in amounts required to prevent or treat shock as seen in acute deficiency These agents are required along with electrolytes in selected cases of acute hypertonic dehydration

In the treatment of a combined water and salt deficiency, it may be necessary to give large quantities of 0 9 per cent saline solution Hypertonic sodium chloride solution is advised when sodium deficit is predominant Many patients with water and salt depletion also lose large amounts of potassium, therefore, this agent is also given in conjunction with sodium chloride In alkalosis and potassium depletion, a condition seen in surgical patients on continuous suction drainage, a mixture of sodium chloride and potassium is superior to the normal saline solution The dangers of overloading the potassium are decreased when these solutions are given slowly during the first 24 hours, and if the total deficit is replaced in a three to four-day period rather than in the first 24 hours

If acidosis is present, sodium chloride or Hartman's lactated Ringers' solution and sodium chloride are the mixtures to be given The various solutions required for the different types of fluid and electrolyte disequilibriums are shown in Table XXII from Moyer

Intravenous Alimentation *Parenteral feeding has been restricted* in the past to water, salt and dextrose However, recent advances have increased the armamentarium of fluids available for parenteral nutri

TABLE XXI

CLASSIFICATION OF CLINICAL DISORDERS OF FLUID AND ELECTROLYTE BALANCE*

Water Disequilibria	*Salt Disequilibria*
1 Acute water deficit	1 Extracellular salt water deficit
2 Chronic water deficit	2 Extracellular salt water deficit with water deficit
3 Absolute water excess	3 Extracellular salt water deficit with relative water excess
	4 Extracellular salt water excess
	5 Extracellular salt water excess with relative water deficit
	6 Extracellular salt water distributional shifts
	7 Any of above (1, 2, 3, 4, 5, 6) with changes in base-bicarbonate (alkalosis or acidosis)

* Intracellular salt disequilibrium states are not considered in constructing this table (Moyer, C *Surg, Gynec & Obst, 84*)

under measurements of blood hydration Even though great emphasis has been placed on laboratory methods for controlling fluid balance or estimating dehydration, there is no universally applicable method and the clinical detection of fluid disequilibrium states is of great importance

In dehydration, there is a change in volume and electrolyte concentration which is just as important as the changes in acid-base balance In most instances, dehydration involves a decrease in electrolytes as well as water However, a greater loss of water than electrolyte is termed hypertonic dehydration Patients or animals with hypertonic dehydration may show an increase in the concentration of electrolytes in the serum, symptoms of shock, evidence of cerebral damage, which is characterized by high temperature and respiratory paralysis, and even death On the other hand, when the loss of electrolyte is greater than the loss of water, the type of dehydration is described as hypotonic The blood changes are revealed as a decreased sodium chloride with an increased concentration of hemoglobin and serum proteins Experiments in animals, performed to elaborate the clinical signs of hypotonic dehydration, show that the animals were sick, refused food and were weak There was also a decrease in the urine volume, decrease in rate of glomerular filtration, and elevation of the nonprotein nitrogen Hypotonic dehydration is characterized by loss of extracellular electrolytes, that is, a dehydration which follows a loss of proportionately more electrolyte than water The picture of hypotonic shock is called

medical shock and responds best to blood, plasma and electrolytes

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TABLE XXII

TREATMENT OUTLINE

Fluid Volume State	Repair Solution	Concentration of Solute in Repair Solution	Composition of Repair Solutions — Compositional Change in Extracellular Fluid: Alkali Normal	Alkali Deficit† (Minimal-Moderate)	Alkali Excess† (Minimal-Moderate)
Acute water deficit	Glucose in water	5, 10, or 15%			
Chronic water deficit; Extracellular salt water deficit with water deficit	Sodium salts	100 mEq /liter*	Sodium chloride plus sodium bicarbonate (or lactate) plus potassium chloride Ratio NaCl NaHCO₃ KClmEq 4 1.0 0.166		Sodium chloride
Water excess	Sodium salts	180 to 360 mEq /liter	Sodium chloride plus sodium bicarbonate (or lactate) plus potassium chloride Ratio NaCl NaHCO₃ KClmEq 4 1.0 0.166		Sodium chloride
Extracellular salt water deficit with relative water excess	Sodium salts	160 to 250 mEq /liter	Sodium chloride plus sodium bicarbonate (or lactate) plus potassium chloride Ratio NaCl NaHCO₃ KClmEq 4 1.0 0.166		Sodium chloride
Extracellular salt water distributional shifts	Sodium salts	100 to 160 mEq /liter	Sodium chloride plus sodium bicarbonate (or lactate) plus potassium chloride Ratio NaCl NaHCO₃ KClmEq 4 1.0 0.166		Sodium chloride
Extracellular salt water excess with or without a relative water deficit	Glucose in water	10 to 15%			

* Salt dissolved in water or in 5 per cent glucose solution

† When disturbed fluid volume states coexist with severe compositional disturbances, the initial treatment should be directed toward the correction of the alkalosis or acidosis

(Moyer, C A *Surg, Gynec & Obst*, 84)

tion Today parenteral proteins are supplied to patients through the intravenous, subcutaneous, or intramuscular routes, as enzymatic or acid hydrolysates of bovine plasma, casein, fibrin, or as pure amino acids About 2 grams of protein to 100 calories metabolized is the usual amount given in 24 hours. These proteins are combined with water, dextrose and electrolytes so as to meet the daily expenditures of these substances One thousand cubic centimeters of a 5 per cent enzymatic hydrolysate of bovine plasma and 50 grams of dextrose will supply a patient with 50 grams of digested protein, 400 calories and 2 5 to 3 grams of sodium as chloride, phosphate and carbonate Hence, three bottles per day in the average adult requiring total parenteral therapy will supply 3000 cubic centimeters of fluid, 1200 calories, 150 grams of protein, or 2 2 grams protein per kilogram for a 70 kilogram subject, and 6 to 8 grams of sodium These figures fit well with the normal daily expenditures of fluid and electrolytes of surgical patients Nitrogen equilibrium in both normal and postoperative patients may be met with the use of these protein solutions

Intravenous fats have been used for supplying calories, but this work is still experimental.

Dextrose in water, 5, 10, or 15 per cent, is the most effective method of supplying calories and water The indications for dextrose as described by Weinstein are (1) to replace acute glycogen deficiency which may occur after surgery, (2) to prevent starvation ketosis, (3) to minimize the protein catabolism by virtue of its protein sparing effect (4) to correct acute hypoglycemia, (5) to help correct water dehydration, since a portion of the dextrose metabolized yields water, and (6) to supply calories necessary for the maintenance of the patient

The rate of tolerance for dextrose was originally set at 0 85 grams per kilogram per hour Recent publications indicate a tolerance rate nearer 0 5 grams per kilogram per hour Weinstein reports a 6 per cent loss of the dextrose injected in patients when 50 grams of 1000 cubic centimeters of dextrose in saline are administered at an average rate of 0 77 grams per kilogram per hour The low tolerance to dextrose, both in healthy and postoperative individuals, requires prolonged infusions if an adequate number of calories as dextrose are to be administered Weinstein's recent studies with invert sugar as a substitute for dextrose are encouraging He reports that 100 grams of invert sugar may be given to humans at a controlled rate of 1 5 grams per kilogram per hour in a single intravenous injection with a 98 4 per cent retention of the amount infused The 100 to 200 grams of carbohydrate required to prevent ketosis therefore may now be given in one to two hours when

TABLE XXII

TREATMENT OUTLINE

Fluid Volume State	*Repair Solution*	*Concentration of Solute in Repair Solution*	*Composition of Repair Solutions* — *Compositional Change in Extracellular Fluid*: *Alkali Normal*	*Alkali Deficit*† *(Minimal-Moderate)*	*Alkali Excess*† *(Minimal-Moderate)*
Acute water deficit	Glucose in water	5, 10, or 15%			
Chronic water deficit Extracellular salt water deficit with water deficit	Sodium salts	100 mEq /liter*	Sodium chloride plus sodium bicarbonate (or lactate) plus potassium chloride Ratio NaCl $NaHCO_3$ KClmEq 4 1 0 0 166		Sodium chloride
Water excess	Sodium salts	180 to 360 mEq /liter	Sodium chloride plus sodium bicarbonate (or lactate) plus potassium chloride Ratio NaCl $NaHCO_3$ KClmEq 4 1 0 0 166		Sodium chloride
Extracellular salt water deficit with relative water excess	Sodium salts	160 to 250 mEq /liter	Sodium chloride plus sodium bicarbonate (or lactate) plus potassium chloride Ratio NaCl $NaHCO_3$ KClmEq 4 1 0 0 166		Sodium chloride
Extracellular salt water distributional shifts	Sodium salts	100 to 160 mEq /liter	Sodium chloride plus sodium bicarbonate (or lactate) plus potassium chloride Ratio NaCl $NaHCO_3$ KClmEq 4 1 0 0 166		Sodium chloride
Extracellular salt water excess with or without a relative water deficit	Glucose in water	10 to 15%			

* Salt dissolved in water or in 5 per cent glucose solution

† When disturbed fluid volume states coexist with severe compositional disturbances, the initial treatment should be directed toward the correction of the alkalosis or acidosis

(Moyer, C A *Surg , Gynec & Obst , 84*)

GASTROINTESTINAL FLUIDS

Osmotic Pressure and Chemical Composition of Gastrointestinal Fluids The digestive secretions of the alimentary tract, with the possible exception of saliva, are all isotonic with the blood serum, in spite of the diversity of their chemical patterns The greater part of these fluids which flow into the gut are subsequently reabsorbed

Such diverse fluids as blood serum, lymph and gastric juice are in osmotic equilibrium Obviously, therefore, equality of osmotic pressure does not signify similarity of chemical pattern

Substances introduced into the alimentary tract from outside the body are rendered isotonic with the blood serum in the course of their absorption. The general isotonicity of the digestive secretions indicates that the digestive glands are incapable of performing osmotic work, though their secretions are not simple filtrates since they differ so greatly in chemical composition Saliva has a lower osmotic pressure and a different inorganic chemical pattern than serum

Gastric and Pancreatic Juices Alterations of the osmotic pressure of the blood are accurately reflected in the gastric juice In the gastric juice isotonicity with the serum is maintained chiefly by changes in chloride concentration whereas in the pancreatic juice sodium bears the chief responsibility for the maintenance of osmotic equilibrium The concentration of sodium in the pancreatic juice bears a relation to the rate of secretion.

Bile Bile as secreted by the liver though isotonic with serum contains more base than serum Its anion pattern is more variable than that of gastric or pancreatic secretion Gallbladder bile becomes concentrated by the absorption of water and electrolytes, e g , bicarbonate and chloride yet the bile remains isotonic with serum. The action of the gall bladder upon the bile consists of the withdrawal of water, chloride, bicarbonate and bases other than calcium In the gallbladder the concentration of bile salts rises The concentration of calcium in the bile is greatly increased in the gallbladder, but this is only a relative increase due to the reabsorption of water probably a small amount of calcium is reabsorbed too Both liver bile and gallbladder bile are more alkaline than serum, their high base content is evidenced by the large amounts of bicarbonate which they hold in combination

Intestinal Fluids The chemical composition of the intestinal secretions changes progressively in character from above downward, though all are isotonic with serum and have sodium as their chief basic ion Jejunal secretion is slightly acid its chief radical being chloride Lower in the bowel the secretion becomes progressively more alkaline

invert sugar is used A comparative study of dextrose and invert sugar with similar rates of 1 5 grams per kilogram per hour in 100 gram doses into the same patients by the above worker showed a 25 to 30 per cent loss with the dextrose, but only a 2 to 4 per cent loss with invert sugar Invert sugar may be a practical and simple substitute for dextrose in carbohydrate therapy

Shock is best prevented or treated by 15 cubic centimeters per kilogram of whole blood given rapidly Whole blood is indicated when red cell and plasma volumes are decreased It increases the oxygen-carrying capacity of the vascular bed The effectiveness of electrolytes in dehydration is enhanced when blood or plasma are also administered

Plasma, either liquid or reconstituted from frozen or lyophilized, is by far the best blood substitute Plasma should not be pooled in its preparation because of the dangers of homologous serum hepatitis Serum is almost as efficient as plasma as a blood substitute Human serum albumin is a concentrated solution which has a greater effect on the oncotic pressure in the vascular compartment This excerpt from Darrow and Pratt describes a method for calculating total fluid requirements "For each 100 calories metabolized, water requirement lies between 90 and 125 milliliters Ten to twenty milliliters may be given as isotonic sodium chloride solution or as 'K-lactate' and the rest as 5 or 10 per cent dextrose in water Two grams of amino acids may be added to the fluid in appropriate cases "

If circulatory disturbances and shock exist with electrolyte deficits, blood and sodium chloride solutions are necessary in the initial treatment

If acidosis is present, a mixture of one part sodium lactate and two parts isotonic sodium chloride is indicated for adequate therapy When potassium deficiency is associated with acidosis, the potassium lactate mixture of Darrow is a satisfactory solution If gastric alkalosis exists, the therapeutic solution is usually sodium chloride In the event that the body potassium is also decreased, this substance is added to the salt solution

If hypertonic dehydration is found, six molar lactate solution is prescribed

The aim of fluid therapy is to maintain normal, chemical fluid and nutritional composition of tissues and to restore all deficiencies to physiological levels

With this hypothesis it is hard to understand how the mucosa decides in which direction to secrete at a given time. The signal for reabsorption to begin can hardly be the completion of the "naturalization" of the foreign solution, for in that case the presence of any of the intestine's own secretion in the bowel lumen would be a stimulus to absorption even in the absence of any foreign material, and secretion would always be checked as soon as it started. It is more probable that normally fluids are adjusted to the proper composition and osmotic pressure in one portion of the gut and then undergo reabsorption at a lower level. At any rate the process of chemical adjustment and the progress of the material along the alimentary tract occur simultaneously and are closely coordinated with each other.

Absorption of Hypotonic and Hypertonic Solutions. Very little water can be absorbed by the stomach. In the intestine, water can pass freely in either direction across the mucosa in accordance with the demands of osmotic equilibrium, that is, for the adjustment of osmotic pressure and chemical pattern of the intestinal contents, whether the latter be hypertonic or hypotonic. These adjustments are effected by simultaneous absorption and secretion. A hypertonic solution may be rendered isotonic by absorption of some of its solute or by secretion of water or a hypotonic solution. Conversely, a hypotonic solution may be rendered isotonic either by the absorption of water or by secretion of solutes into it. At successively lower levels of the gut the tendency to make adjustments by means of the absorption of fluid increases progressively while secretion diminishes.

Dextrose Absorption by the Colon. Small amounts of dextrose may be absorbed by the colon, but it is absorbed so slowly and to such a slight extent that its rectal administration for the purpose of feeding is of no appreciable value. It is doubtful whether more than minute traces of dextrose ever reach the lumen of the colon under ordinary normal conditions.

Absorption of Fats and Lipoids. Fats and lipoids cannot be absorbed unless they are first rendered miscible with water by the action of bile and pancreatic juice. They are not absorbed by diffusion for they probably do not go into true solution, and because of their large molecular size the vascular endothelium is impermeable to them in the colloid state. The method by which fats and lipoids are transported across the wall of the intestine is obscure. They do not enter the portal circulation but only the lymphatics.

Role of Sodium and Chloride in Absorption. Adjustments of the osmotic pressure of the intestinal contents are effected chiefly by means

TABLE XXIII

ACID OR BASE PREDOMINANCE OF FLUID IN VARIOUS SECTIONS OF THE GASTROINTESTINAL TRACT
(in milliequivalents)

Portion of GI Tract	*Total Base*	*Cl*	*HCO_3*
Fundus gastric juice	40	160	
Pylorus juice	188	142	
Hepatic bile	182	90	45
Pancreatic juice	168	115	45
Duodenum	177	120	
Jejunum	155	150	20
Ileum	162	80	90
Colon	160	80	92

(Coller and Maddock *Surg, Gynec & Obst, 70*)

and bicarbonate gradually replaces chloride as the acid radical The acid and base milliequivalents of fluids in various sections of the gastrointestinal tract are shown in Table XXIII

The total volume of digestive secretions in 24 hours, for an average adult, is large These figures are estimates for the daily secretions 1500 cubic centimeters saliva, 2500 cubic centimeters gastric juices, 500 cubic centimeters bile, 700 cubic entimeters pancreatic juice, 3000 cubic centimeters intestinal mucosa secretions—a total of 8200 cubic centimeters The gastrointestinal secretions represent three times the average quantity of fluid taken by mouth Disturbances in gastrointestinal circulation are of great significance to the surgeon

The Mechanism of Absorption · Solutions introduced into any part of the intestinal canal, as a preliminary to absorption, are readjusted in osmotic pressure to isotonicity with the blood serum and in electrolyte pattern so as to resemble the secretion normally produced at that level of the alimentary tract

The reduction of serum electrolytes that follows the ingestion of a large volume of distilled water is referable to passage of salt into the gut as it is to absorption of water into the blood Since the foreign solution introduced ultimately attains the same composition as the digestive fluid normally secreted into the lumen of the bowel, the final step of absorption is equivalent to a reverse secretion, from the bowel lumen to the blood stream, of a fluid similar to the normal external secretion of the intestinal mucosa It appears, therefore, that the mucous lining of a given portion of the intestine is capable of secreting the same fluid toward the lumen at one time and away from the lumen at another time

related to absorption represent work performed by it, even if the ingested substances are fluids only He expresses the opinion that confining the gastrointestinal intake to fluids, and especially to water, does *not* provide rest for the alimentary canal He states that introducing only physiologic isotonic solutions into the alimentary canal is the best way to minimize dehydration and salt depletion and to diminish the requirements for parenteral fluids, especially in obstruction or fistulous opening of the gastrointestinal tract. The maximum rest for the alimentary canal is achieved by giving nothing at all by mouth Even an indwelling tube may stimulate secretion

Peters found that in dogs with the pylorus ligated vomiting ceased if no water or food was given by mouth. He observed that the introduction of water into the bowel or stomach in obstruction or fistula seems to provoke the excretion of additional water as well as salt He states that it is next to impossible to establish salt and water equilibrium or a positive balance by this method, all the fluids entering the mouth and most of those given parenterally are likely to be excreted, either by excretion into the bowel lumen, or by loss through the fistula or through suction drainage He believes that in the employment of the Wangensteen apparatus for suction drainage, less water and salt might be lost in the drainage if the fluid given by mouth contained salt He mentions that water introduced directly into the ileum has a peculiarly injurious effect on the mucosa of the latter In general, Peters stresses the desirability of making all food or fluids that enter an irritable or diseased intestine isotonic with serum by means of sodium chloride, in order to allay secretory and motor activity of the gastrointestinal tract, promote absorption and mitigate dehydration and salt depletion

Calcium, Magnesium and Phosphorus Excretion The bowel is the chief channel for the excretion of calcium and an important one for the excretion of phosphorus Part of the fecal calcium and phosphorus is endogenous these substances are largely absorbed in the upper part of the intestine and re-excreted into the gut at a lower level The absorption and excretion of calcium is greatly influenced by the action of the antirachitic vitamin Increased acidity of the blood, i e, decreased alkaline reserve accelerates calcium absorption The intestinal contents from which calcium is absorbed are normally alkaline and apparently do not become less alkaline at times of accelerated calcium absorption Calcium and magnesium are the chief basic inorganic ions of feces, and phosphate and carbonate the chief acid radicals Feces contain very little sodium potassium or chloride

Loss of Water Sodium and Chloride In view of their high con

of changes in the concentration of sodium and chloride Diffusion of these two ions seems to be controlled more by the total osmotic pressure than by their own activities in the fluid media of the body In successively lower segments of the intestine the fluid poured into the bowel for the osmotic adjustment of a foreign salt solution contains less and less chloride and proportionately more sodium The nature of the acid radical seems to be more subject to variation than that of the base, for sodium serves as the alkaline osmotic equalizer in all segments of the gut, whereas the acid radical cooperating with it is chiefly chloride in the upper part of the intestine and chiefly bicarbonate lower down.

Loss of Gastrointestinal Fluids· Nadler points out that certain mechanical factors make the digestive fluids liable to depletion, namely 1 Loss from the upper part of the gastrointestinal tract (fistula, obstruction) 2 Exclusion from the absorptive area (obstruction) 3 Non-entrance into the intestine (biliary and pancreatic fistula) 4 Excess motility of the bowel The results of such losses upon the body are (1) depletion of water, (2) diminution of total electrolytes, (3) alteration of the electrolyte pattern, especially with regard to the balance between acid and basic radicals, (4) azotemia, due to inadequate fluid for excretion, retention of metabolites in an effort to replace lacking salts by other solids, and combustion of body proteins due to starvation, (5) ketosis, due to starvation with consequent combustion of body fats Both salt solution and glucose solution are necessary to treat properly the patient suffering from electrolyte and fluid imbalance Salt solution will correct best water depletion, diminution of total electrolytes and alteration in the electrolyte pattern Glucose solution can prevent the ketosis due to fat combustion in the starved patient.

Effects on Electrolyte Pattern. In loss of gastric and intestinal secretions, the acid loss (gastric chloride) may balance the base loss (pancreatic and intestinal bicarbonate), more often, the loss of one or the other will predominate, depending on the level of the obstruction, the relative interference with secretion versus absorption, the nutritive state of the tissues and a number of other uncontrolled factors Consequently any prediction of the resultant electrolyte pattern is hazardous and is not a suitable basis for rational treatment The pattern may suffer little disturbance if the obstruction is in the lower colon, distal to the absorptive area No precise knowledge of the electrolyte pattern is needed for treatment because of the fact that the kidney, if supplied liberally with both sodium and chloride, has an extensive capacity to make any required corrections in the electrolyte pattern

Peters (1940) points out that the activities of the alimentary tract

In many cases there was no vomiting, the fluid lost from the blood and tissues remaining within the lumen of the alimentary tract

SWEAT

In addition to salt, sweat contains considerable amounts of nitrogen, chiefly in the form of urea, and lactic acid It does not contain sugar In its inorganic pattern sweat resembles interstitial fluid

Heat Elimination by Sweating The excretory function of the skin seems to be devoted to the regulation of body temperature rather than to elimination of water or solids Under basal conditions, about 25 per cent of heat elimination is accomplished by vaporization In insensible perspiration the salt loss is negligible, for the skin can give off water as vapor without appreciable amounts of salt Up to a certain point the loss of insensible perspiration from the skin does not involve a process of secretion for it occurs in the absence of sweat glands The sweat glands, acting primarily in behalf of temperature regulation, cause the loss of salts essential for the body economy merely because of the difficulty of separating pure water from the salt-containing fluids of the body That no useful purpose is served by the excretion of the salt is indicated by the fact that in persons in good physical training the salt content of the sweat is reduced. The elimination of waste products such as lactic acid and nitrogenous substances is only a subsidiary and poorly developed function of the sweat glands, and one which is performed much more effectively by other organs of the body, particularly the kidney

Water and Salt Elimination by Sweating Sweating can be the primary cause of marked depletion of salt and water The skin can excrete as much as 2 grams of salt per hour in profuse sweating The coincident loss of water is relatively greater, since sweat is hypotonic The net result would be to leave in the tissues an excess of salt which would render them hypertonic, but this is prevented by the kidneys which excrete the excess salt in hypertonic solution, that is with a minimal loss of water Ultimately, therefore, loss of a liter of sweat deprives the body of a liter of isotonic saline It does not however disturb the electrolyte pattern of the blood serum, because the pattern of sweat is the same as that of serum.

Salt Depletion from Sweating Miners' cramps are caused by excessive dilution of body fluids with water after the salt content of the body has been depleted by profuse sweating They are a manifestation of water intoxication, which means merely reduction of the osmotic pressure of the body fluids, both extra and intracellular Miners

centrations of sodium or chloride or both, the gastrointestinal secretions, though formed immediately from the blood, must be derived chiefly from the interstitial fluid reserve of the body The normal secretory activity of the stomach after meals may cause detectable changes in the inorganic chemical pattern of the blood These alterations are rather small probably because of restoration of the blood by interchange with the interstitial fluid. They are transitory because the acid gastric secretion, after performing its digestive function, is passed into the intestine where it is neutralized and then reabsorbed If its passage into the intestine and consequently its reabsorption is prevented, as by pyloric obstruction, the alteration in the composition of the blood and of the interstitial fluid becomes permanent, and, if secretion continues, progressive The change consists of a loss of water, chloride and sodium, the loss of chloride being greater than that of sodium As a result the concentration of sodium in the serum and interstitial fluid becomes too high with reference to that of chloride, markedly excessive alkalinity of these fluids is prevented by neutralization of the excess sodium by carbonic acid The final effect of pyloric obstruction on the blood serum, therefore, is deficiency of chloride and excess of sodium and bicarbonate, with an appreciable increase in alkalinity These changes can occur without actual vomiting, if the gastric secretion accumulates in the stomach

Pancreatic and Intestinal Fistula Fluid lost through a fistula of the pancreas or intestine contains more sodium than chloride The effect of this loss upon the serum is an increased concentration of chloride and a decreased concentration of sodium and bicarbonate, with an appreciable increase of acidity Diarrhea produces a similar picture, partly because the feces are normally alkaline, and partly because the still more alkaline contents of the small bowel are prevented from being reabsorbed

Saline Administration in Intestinal Obstruction From experiments on dogs Hartwell and Hoguet (1912) concluded that loss of fluid is the important factor in explaining the symptoms and death following uncomplicated high intestinal obstruction They found that death could be prevented by replacing the water lost through vomiting by means of subcutaneous injections of normal salt solution If untreated dogs lived only 3 to 10 days, with saline injections exceeding in amount the total loss of water in the vomitus and the urine, they lived three weeks or longer, a period corresponding to the survival period in simple starvation The amounts of solution given the dogs would correspond to 5 to 10 liters per day for a man of average size

the activity, the lower is the protein content of the lymph which flows from the active part In the lymph vessels of the active limb of the dog the pressure may, against obstruction, rise as high as 95 centimeters of water The efficiency of lymphatic drainage affects the amount of inter stitial fluid in a part

Perfusion of isolated organs experimentally under constant pressure often leads to edema A pulsate pressure seems to be necessary for adequate interstitial lymph drainage

Serum, because of its higher colloid content, contains less water and, therefore, less solutes than either interstitial fluid or lymph, although all three fluids are in osmotic equilibrium The origin of the serum proteins is obscure They cannot gain access to the circulation directly, since the blood capillary endothelium (at least in most parts of the body) is impervious to them Therefore, unless they are formed in the blood itself they must be conveyed to it by the lymph Thompson *et al*, found that hypoproteinemia produced experimentally in dogs frequently caused disruption of operative wounds lyophile serum was beneficial in counteracting this harmful effect of the hypoproteinemia Edema resulting from deficiency of serum protein is more dependent on the level of the albumin fraction than on that of the globulin fraction, due to the fact that the albumin is present in greater amount and exerts a greater osmotic pressure per gram (7 54 centimeters of water) than does globulin (1 95 centimeters of water) In lymph, albumin constitutes an even greater proportion of the total than it does in the blood serum.

TRANSUDATES

Effusion and reabsorption of colloid free fluids in the serous cavities are believed to be determined largely by the same forces concerned in the exchanges between the blood and the interstitial spaces Colloidal substances and particulate material, in contrast to the electrolytes, can be absorbed from the serous cavities only by the lymphatics, water and electrolytes can be absorbed by both the blood stream and the lym phatics

Peritoneal fluid usually has less protein than pleural fluid Edema fluid generally contains less protein than fluid from serous cavities

Transudates generally contain more chloride than blood serum, but less calcium and potassium, sodium bicarbonate and phosphate are quite evenly distributed The same statements are true of normal inter stitial fluid Serum ultrafiltrates in general contain more chloride and bicarbonate and less base per unit of water than serum itself The low serum chloride content in certain clinical conditions, such as intestinal

cramps cannot occur in the dog, because of the absence of sweat glands

Since much more salt is excreted in the urine than in the sweat, it might seem reasonable to expect a more severe degree of salt depletion to occur as a result of diuresis than as a result of marked sweating Yet water intoxication in consequence of urinary salt loss is not observed The noxious effect of loss of salt in the sweat depends on the fact that the excretion of salt by the sweat glands is not a purposeful function regulated in accordance with the salt requirements of the body, but rather an adventitious and wasteful excretion unavoidably associated with the elimination of water for the dissipation of heat—the latter being the function to which the activity of the sweat glands is attuned The sweat glands are unconcerned about the osmotic pressure of the blood The kidney, on the contrary, has as one of its special duties the safeguarding of the osmotic pressure of the body fluids, therefore, it varies its activity with particular reference to the needs of the body for salt and water It excretes less salt whenever there is any danger of depleting the salt supply in the body

List and Peet report studies on various aspects of the physiology of sweat secretion

White (1939) discussed the treatment of hyperhidrosis by sympathectomy

THE LYMPHATICS

The lymphatics can carry materials in only one general direction, namely from the tissues to the blood, but they are a secondary or accessory transportation system, since it has been shown that fluid can pass from the tissues directly into the blood stream The presence of the two systems suggests functional differentiation The distinctive function of the lymph capillaries is the removal from the tissues of particulate or colloidal material which is precluded from entrance into the blood capillaries This function is performed, for example, in the lymphatic absorption of transudates and exudates and also in the absorption of lipoids from the intestine The walls of the lymph vessels have been shown to have irreversible permeability to particulate foreign material of large size, and they probably have the same relation to all colloids, for the lymphatic system would be ill adapted to its function if, when substances had been collected within the vessels, they were unrestrained and likely to escape again

The lymph system is accelerated by physical activity, it flows only slowly or nearly ceases when the part it drains is at rest It is hardly conceivable that the lymph flow ceases entirely during rest The greater

fluid in the serous body cavities Possibly the relative protection against infections which are conducive to the formation of edema is due to the fact that the fluid is enclosed in a quiet inelastic case It is relatively uninfluenced by changes of serum protein concentration Yet to maintain the isotonicity which it has with the blood serum, the spinal fluid has to be responsive to changes in the total (as distinguished from the colloid) osmotic pressure of the serum This is found to be the case, for the volume of the cerebrospinal fluid is altered temporarily when hypertonic or hypotonic solutions are injected into the blood stream In summary, Peters states that the cerebrospinal fluid "is confusingly similar to serum ultrafiltrates but has distinctive features which indicate that the lining membrane of the choroid plexus has a selective capacity which differentiates it" from the other serous membranes

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obstruction, is associated with an exaggeration of this unequal distribution of the chloride ion between the serum and the interstitial fluid

SYNOVIAL FLUID

Synovial fluid contains some mucoprotein, the origin of which is obscure for it is not present in the blood, and there are no mucous glands in the synovial membranes In other respects synovial fluid has the characteristics of a simple ultrafiltrate of serum The pattern of electrolytes in joint fluid closely resembles that of serum Glucose and the nonprotein nitrogenous substances diffuse into the joint cavities rather freely. Proteins can escape from the synovial cavities only by way of the lymphatics, just as in the case of serous body cavities and the interstitial spaces

CEREBROSPINAL FLUID

Chemical Composition of Cerebrospinal Fluid· The chemical composition of cerebrospinal fluid obtained by lumbar puncture differs appreciably from that of fluid obtained simultaneously by ventricular tap Filtration from the blood stream into the cerebrospinal fluid is believed to occur only at the choroid plexus, hence in its slow passage from the brain down along the spinal cord the fluid suffers reabsorption of some of its solutes, especially glucose Serum and spinal fluid have equal osmotic pressures Isotonicity is not of itself evidence of origin by filtration since various fluids known to be formed by secretion, e g, gastric and pancreatic juices, are in osmotic equilibrium with the blood serum The electrolyte pattern of the spinal fluid closely resembles that of serum ultrafiltrates, transulates and lymph Changes in serum calcium content induced by such measures as calcium administration or parathyroid administration or deprivation, though they are accurately reflected in the calcium content of other body fluids, produce little alteration in spinal fluid calcium The same is true in conditions of spontaneous hyper- and hypocalcemia, including tetany

Mechanism of Cerebrospinal Fluid Formation· The available evidence indicates that cerebrospinal fluid is not simply a protein-free ultrafiltrate of blood serum, but a much more highly differentiated fluid Consequently the forces which control its production are presumably different from or more complex than those which govern the exchanges of fluid between the blood and the interstitial spaces In systemic disorders marked by transudates resulting from disturbances of the normal relation between hydrostatic and colloid osmotic pressure, spinal fluid is usually not increased in amount as are the interstitial fluid and the

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Chapter XIV

ACID-BASE BALANCE

MAINTENANCE of normal acid-base balance depends upon two types of mechanisms, one consisting of strictly physical and chemical processes, in which carbon dioxide plays a conspicuous part by reason of its peculiar properties, the other type being physiological or "vital" activities on the part of certain organs, notably the lungs and the kidneys

The precise meaning of the familiar term pH can best be kept in mind by memorizing its definition, namely *"pH is the logarithm of the reciprocal of the hydrogen ion concentration"*, ($pH = \log \frac{1}{[H^+]}$) The derivation of the term is as follows The letter *p* is used (instead of the letter *l*) to denote logarithm, it stands for "power" (in German, "potenz"), that is, "the power to which 10 must be raised " The *reciprocal* of the hydrogen ion concentration is used instead of the actual concentration because the latter is usually a very small figure, far below unity, and has therefore a negative logarithm For example, in a given solution if there is one gram of hydrogen ions in every 10,000,000 grams of solution, the hydrogen ion concentration is $\frac{1}{10{,}000{,}000}$ The logarithm of this fraction has the disadvantage of being a negative figure, —7 In the term pH, the minus sign is dropped as a matter of convenience, but whereas —7 is the logarithm of $\frac{1}{10{,}000{,}000}$ (the *actual* hydrogen ion concentration), +7 is the logarithm of $\frac{10{,}000{,}000}{1}$ i e , the *reciprocal* of the hydrogen ion concentration

To replace the cumbersome expression "hydrogen ion concentration," the symbol $[H^+]$ is used at times in the following discussion (The writer invented the term "hydrition" as a substitute for "hydrogen ion concentration" but abandoned it on competent advice, though it *does* save six syllables)

The material in this chapter is derived largely from Peters and Van Slyke

PHYSICAL AND CHEMICAL FACTORS IN ACID BASE BALANCE

Role of Carbon Dioxide Regulation of the hydrogen ion concentration of the blood is intimately related to the chemistry of respiration, largely because of the prominent role of CO in both functions Carbon dioxide is in a sense the greatest problem in the regulation of neutrality of the blood, for it is the acid which enters the blood in the greatest amounts The most important chemical reactions by which this acid metabolite is buffered, that is, prevented from having its full acidifying effect upon the blood, are those described above in connection with CO transport Quantitatively the most important single factor in that respiratory process is the isohydric accommodation of large amounts of CO_2 by hemoglobin, by reason of the decrease in acidity which occurs when oxyhemoglobin loses its oxygen

Volatility of CO_2 But carbon dioxide may also be considered the chief item in the solution of the problem of acid base balance, mainly by reason of its constant *availability* and of a unique special virtue which it has, namely the physical property of *volatility* Most of the CO_2 present in the blood at any given moment exists in the form of sodium bicarbonate $NaHCO_3$ If any acid stronger than carbonic acid enters the blood it immediately reacts with the sodium bicarbonate, displacing the weaker acid H_2CO_3 but being itself neutralized by combination with the freed alkali It is impossible therefore for the blood to contain any acid stronger than CO_2 as long as any $NaHCO_3$ remains The CO_2 liberated in this manner, though weaker than the acid which has seized its alkali, is nevertheless capable of disturbing the reaction of the blood if it remains in the blood stream But the crux of the matter is that it does not remain The excess of CO_2 in the blood raises the CO_2 tension in the latter, therefore diffusion into the alveolar air, in which the CO_2 tension is lower than in the blood, occurs at an increased rate, and quickly removes the excess of CO_2 from the blood

Practically all the other acids formed by metabolism in the body, whether organic or inorganic, are stronger than carbonic acid

Availability of CO_2 as Blood Bicarbonate Carbon dioxide is continuously produced by the processes of combustion in the tissues and is evolved so rapidly that any alkali which gains access to the body is immediately and automatically neutralized by being converted into bicarbonate. The bicarbonate of the blood represents the excess of base over all acids other than carbonic acid. This base is uniquely available to neutralize any increase of these acids because the CO_2 in the bicar

bonate is (1) so readily displaced, being a weak acid, and (2) so easily removed, being volatile Therefore the bicarbonate is termed the alkali reserve

Determination of [H˙] from CO Values A solution of free CO_2 is acid, a solution of sodium bicarbonate is alkaline in reaction The blood contains both The [H˙] of a solution containing both free carbonic acid and sodium bicarbonate must lie somewhere between that of the separate solutions, at a point determined by the relative proportions of the two substances, that is, it is proportional to the ratio of H_2CO_3 to $NaHCO_3$, the more the former the higher the acidity [H˙], and vice versa. It is feasible therefore to estimate the hydrogen ion concentration of physiological fluids by determination of the relative concentrations of carbonic acid as such and of sodium bicarbonate

Because of certain disadvantages of measuring the concentrations of these substances directly, indirect methods are commonly employed in practice Carbonic acid H_2CO_3 is composed of water and CO_2



$$H_2O + CO_2 = H_2CO_3$$

The gas CO_2 readily escapes from this combination when the latter is exposed to an environment containing a lower concentration of CO_2. This tendency to escape, that is, the "*tension*" or "pressure" which the combined CO_2 gas exerts, is proportional to the concentration of CO_2 and may therefore be used as a measure of the latter The sodium bicarbonate can best be measured indirectly by decomposing it with a strong acid and measuring the *amount* of CO_2 thus liberated

Since the hydrogen ion concentration of the blood is determined by the ratio between the carbonic acid and the bicarbonate, it may be calculated from appropriate measurements of the CO_2 *tension*, representing the carbonic acid concentration, and of the *amount* of CO_2 representing the sodium bicarbonate concentration. In the above discussion the term "sodium bicarbonate" is used for simplicity in place of total bicarbonate, for in the blood a certain amount of other bases besides sodium are combined with bicarbonate, but their behavior is the same with regard to hydrogen ion concentration

In the body the concentration of carbonic acid at any given time depends upon the balance between the rate of production of CO_2 and its rate of loss through respiration The sodium bicarbonate concentration depends upon the amount of alkali in the body over and above that which is combined with non-volatile acids (that is acids other than carbonic acid) The blood cells contain much less CO_2 per unit volume than the plasma The difference is chiefly due to the greater amount of

water in the plasma, and to the fact that as much as half the alkali in the cells may be combined with hemoglobin and therefore is not available to combine with CO_2.

Buffers. A buffer is a mixture of chemical substances which by their presence in solution decrease the change in hydrion caused by the addition of acid or alkali. It consists of a weak acid and its alkaline salt or a weak base and its acid salt. In the body the former occur, the chief ones being $H_2CO_3 + NaHCO_3$, $NaH_2PO_4 + Na_2HPO_4$ and H protein + B protein. Free alkali, such as NaOH, cannot exist in the living body, and therefore is not a practicable means of defense against acids. Moreover, salts of strong acids, such as NaCl, have no neutralizing power, since the acid they would set free (HCl) would itself have a marked effect on the [H] of the body fluids. Therefore, all the physiologically available alkali reserve for the immediate neutralization of acids has to be in the form of buffer salts, that is, salts of weak acids. In the blood the alkali salts of the proteins (including hemoglobin) are the most important of these buffers, quantitatively.

Bicarbonate as Buffer. It is true that the bicarbonate is a potent defense against acid invasion but this is not due so much to its buffer action as it is to the fact that when it is decomposed the acid set free is volatile and leaves the body at once by way of the lungs. Average normal blood contains about 22 millimols of bicarbonate per liter, about 80 per cent of which (18 millimols) is "physiologically available," that is, may be decomposed before the symptoms of acid intoxication become extreme.

Even without the bicarbonate, approximately 25 cubic centimeters of normal acid or alkali must be added to a liter of blood to cause the plasma pH to change 1 unit (from 7 to 6 or 8). In profound acidosis the pH change amounts to only about 0.4 units (from 7.4 to 7.0), therefore approximately 0.4 of 25 cubic centimeters = 10 cubic centimeters of N alkali (= 10 milliequivalents) per liter of blood are utilizable from buffers other than bicarbonate. About 80 per cent (8 milliequivalents) of this physiologically available non bicarbonate alkali is combined with hemoglobin, the remaining 20 per cent being practically all (1.7 milliequivalents) combined with serum proteins. With a total volume of circulating blood of 5 liters, the physiologically available alkali in the blood alone amounts to about 5 × 28 = 140 cubic centimeters of N alkali.

Hemoglobin as Buffer. Bicarbonate is the most important source of alkali for the neutralization of acids in general, but *hemoglobin* is the most important neutralizing factor when the invading acid happens to

be carbonic acid The blood is able, chiefly because of the buffer hemoglobin, to absorb from the tissues and give off in the lungs an amount of carbonic acid which in water or in an unbuffered solution would produce an intolerable degree of acidity The chief reaction by means of which hemoglobin takes part in the neutralization of carbon dioxide may be indicated as follows.



$$H_2CO_3 + KHbO_2 \rightarrow KHCO_3 + HHbO.$$

This reaction consists essentially of substitution of "hemoglobinic acid" (HHbO.) which is a very weak acid, for an equivalent amount of the stronger carbonic acid, H_2CO_3

Tissue Buffers The tissues contain an amount of available alkali estimated at about six times as great as that of the blood, that is about equivalent to 900 cubic centimeters of 1 N acid There is normally enough total available alkali in the body to receive about 1 5 cubic centimeters of 1 N acid per kilo of body weight before the blood or tissue pH falls to a fatal degree. The nature of the tissue buffers is not fully known

PHYSIOLOGICAL FACTORS IN ACID-BASE BALANCE

The principal "physiological" reactions responsible for acid-base balance, as distinguished from the "purely physicochemical" reactions just mentioned, consist of quantitative alterations of the pulmonary ventilation, and both quantitative and qualitative alterations of kidney function

Respiration and Acid-Base Balance: *Respiratory Response to CO_2* The respiratory center is stimulated by any excess of CO_2 tension in the blood, so that breathing is increased and the excess CO_2 is removed, restoring the hydrogen ion concentration to normal This vital reaction by which the alveolar air is renewed therefore supplements the physicochemical process, accelerated diffusion of CO_2 from the blood into the alveolar air, mentioned above

The alveoli may be pictured as a reservoir into which CO_2 is being continuously poured from the venous blood, and from which CO_2 is being continuously washed out by the stream of respired atmospheric air The concentration of, and therefore the pressure exerted by, CO_2 in the alveolar air at any moment is determined by the ratio between these two processes. The arterial blood as it leaves the lungs is ordinarily in exact equilibrium, as to CO_2 tension, with the alveolar air The *amount* of free CO_2 dissolved in the arterial blood depends upon

the pressure of CO_2 in the environment, that is, upon the tension of CO_2 in the alveolar air The alveolar air is the effective gaseous "environment" of the arterial blood being the only gas to which the arterial blood is directly exposed But the tension of CO_2 in the alveoli is regulated by the respiratory activity hence the amount of free CO_2 in the arterial blood is determined by the respiratory activity Since the hydrogen ion concentration of the blood increases with increased content of CO and vice versa, it follows that the [H] of the arterial blood depends upon the CO_2 tension of the alveolar air, and hence upon the respiratory activity

Respiratory Response to Non Volatile Acids When acids other than carbonic acid gain entrance to the blood the same respiratory mechanism responsible for maintenance of normal [H] is activated for the foreign acid decomposes bicarbonate to obtain alkali from it, liberating therefore an equivalent amount of CO_2 Even after the CO_2 thus released is removed by increase of breathing, a certain degree of abnormal acidity remains because part of the bicarbonate of the blood, which is alkaline in reaction having become combined with the foreign acid, is withdrawn from the effective alkali content of the blood This residual acidity can be and is offset by a further increase of breathing sufficient to lower the CO_2 below its original level by an amount corresponding to the amount of alkali that has been appropriated by the foreign acid In this way the normal acid alkali ratio (that is the carbonic acid bicarbonate ratio) is restored to normal, hence normal hydrogen ion concentration is restored When the process is completed, respiratory activity subsides to its normal level If the accession of foreign acid continues, increased respiratory activity continues correspondingly in an effort to compensate Compensation is established when the [H] of the blood is reduced to its original normal level by means of a reduction, through hyperpnea, of carbonic acid equivalent to the reduction of bicarbonate,

The controlling stimulant of respiration in acidosis cannot be CO_2 alone because otherwise the hyperpnea would no longer continue when the blood CO_2 had fallen to and even below the normal level The hyperpnea is ascribed to the increase in [H] induced by the foreign acid It is probable that the hydrogen ion concentration of the cells in the respiratory center is the influence most directly acting on the center, and that a change in [H] of the plasma may not produce immediately a similar change in the [H^+] of the cells in the center

The increase in ventilation provoked by oxygen want during rest

does not usually exceed 50 per cent and is therefore slight in comparison with the several hundred per cent increase that can be caused by breathing air to which CO_2 has been added

Alkalosis from Hyperpnea Hot baths can induce hyperpnea resulting in lowered blood CO_2 tension and decreased [H^+] The preservation of normal body temperature takes precedence over the exact regulation of blood reaction in this case

Respiration has at least five well recognized functions (1) The provision of an adequate supply of oxygen for the body; (2) the elimination of the CO_2 produced by the metabolic processes, (3) the maintenance of a constant reaction in the internal environment, (4) the preservation of body temperature, and (5) regulation of the water content of the body When the need for special activity in any of these functions becomes predominantly urgent, respiration is regulated more especially in accordance with that function and less in accordance with the others than usual The magnitude of the actual respiratory response is not always proportional to the importance to life of the function disturbed in a given case For example, the response to oxygen want is weak compared to the response to CO_2 excess, although life is more endangered by oxygen want than by CO_2 accumulation

Alveolar CO_2 as a Measure of Alkali Reserve Since in acidosis the respiratory exchange increases sufficiently to cause a reduction of the alveolar CO_2 tension, the determination of the extent of the reduction of the alveolar CO_2 tension may be employed as an objective measure of the degree of acidosis (decreased alkali reserve) However, this measure is accurate only if the hydrogen ion concentration of the blood remains normal, which is seldom the case Moreover, the usual close relationship between alveolar CO_2 tension and blood bicarbonate content may be disturbed not only by acidosis but also by alkali therapy, and by disease conditions which impede gas exchange. Therefore the alveolar CO_2 tension can serve only as a very rough indication of the alkali reserve of the blood.

Respiratory Influences on Plasma Bicarbonate Value The plasma bicarbonate content does not reveal accurately the acid-base balance of the blood when the control of respiration by CO_2 tension is interfered with, as for example in the hyperpnea of some febrile and nervous conditions and in the depressed breathing of morphine poisoning However, most clinical conditions of disturbance of acid-base balance are due to retention or loss of nonvolatile acids or bases, and the net effect upon the available alkali buffer reserve is reliably indicated by the plasma bicarbonate content. When, by determination of the plasma bicarbonate

content an abnormality of balance between nonvolatile acids and bases has been demonstrated, it may be of importance, in order to gain more exact knowledge of the chemical pathology of the disease under observation and more specific indications for therapy, to ascertain the particular acid or basic radicals, the excess or deficiency of which is responsible for the abnormality in the total balance

To interpret the plasma bicarbonate content as an indicator of the alkali reserve it is essential that the proportion of alkali combined with hemoglobin be maintained at its normal value or be fixed under definite standardized conditions In the circulating blood, changes of plasma bicarbonate content due to clinically serious acidosis or alkalosis are gross in comparison with variations due to the degree of oxygenation of the blood or to alterations of CO_2 tension The procedure now employed to measure plasma bicarbonate is the determination of the CO_2 content of "true plasma from blood drawn and centrifuged with precautions to prevent loss of CO_2 ' True plasma" is plasma which has been brought into equilibrium with a known tension of CO_2 while still in contact with the blood cells

Variations in oxygenation and in [H] may cause as much as 10 volumes per cent change in the plasma CO_2 content of blood in which the actual acid base balance, aside from the effects of O_2 and CO_2 tensions, has not changed To avoid such effects the blood before analysis must be brought to standard conditions of oxygenation and hydrogen ion concentration, or else the observed CO_2 content must be corrected to these standard conditions The latter procedure is simpler The aim in view is to attain before analysis of the plasma a normal distribution of the buffer alkali between bicarbonate (plasma) and hemoglobinate (red cells) Theoretically the most desired standard conditions are those in normal arterial blood, namely complete oxygenation and pH of 7 4 For practical reasons, however, the conditions usually employed are complete oxygenation and a CO_2 tension of 40 mm at 38° C Because of the difficult technique involved the procedure has not been applied to routine clinical studies

The Kidney and Acid Base Balance The carbonic acid content of the body is regulated chiefly by the lungs the content of all other acids and of the bases is controlled by the kidney, which by varying the composition of the urine according to the relative proportions of acid and basic products, prevents any significant disturbance of the acid base balance of the body fluids

Rôle of Phosphates The response on the part of the kidney in connection with the regulation of acid base balance is necessarily less

prompt than that of the lungs, for the kidney must deal with the numerous nonvolatile substances in the blood, both inorganic and organic, which exert an influence either toward acidity or toward alkalinity The urine becomes more acid to compensate for increased blood acidity, and more alkaline in response to excess alkalinity of the blood The reaction of the urine is altered chiefly by alterations of the relative amounts of the two types of phosphates it contains, namely acid phosphate (NaH_2PO_4) and basic phosphate (Na_2HPO_4) The kidneys do not stop to inquire what specific substance is responsible for a given disturbance of the reaction of the blood and seek out this substance in order to eliminate it Instead they respond promptly by an appropriate adjustment of the acid and basic phosphates, which are substances with which the kidneys are constantly dealing If, for example, some strongly acid substance which gains entrance into the blood stream of such a nature that the kidney is wholly incapable of excreting it, whereas the liver would be able to destroy it in the course of time, it is much better for the kidney to compensate for the general disturbance in hydrogen ion concentration as soon as possible by excreting an equivalent amount of some non-specific acid substance, such as sodium acid phosphate, than to perform no protective function whatever

Acid phosphate, $H(BHPO_4)$, is normally quantitatively the most important acid product excreted In the blood 20 per cent of the total phosphate is in this form and 80 per cent is in the form of the alkaline salt $B(BHPO_4)$ In the urine, therefore, any acid phosphate over and above 20 per cent of the total phosphate represents acid removed from the body without loss of corresponding base The most logical way to measure the total amount of excreted acid is to titrate the urine with alkali from its observed acidity to blood reaction (pH 7 4) The average 24-hour value is 20 to 40 cc of 1 N acid This increases whenever the blood becomes more acid in reaction (pH falls)

CO_2 Excretion in Urine The CO_2 tension of urine is approximately the same as that of the arterial blood, normally about 40 mm. Hg. The CO_2 content therefore is about 1 2 millimols per liter The more alkaline the urine the greater the total CO_2 and bicarbonate content In highly alkaline urines several grams of bicarbonate may be excreted per liter

Excretion of Non-Volatile Acids The only acid which results from normal metabolism of carbohydrates and fats, CO_2, is removed by respiration as fast as it is produced and therefore does not affect acid-base balance The acids from protein metabolism, sulphuric and phosphoric,

have to be excreted in the urine, and base must accompany them to prevent excessive acidity of the urine Organic acids are normally oxidized, except uric acid, which is excreted in amounts too small to affect the general acid base balance Organic acids become of importance only when the body loses its ability to burn them

On an ordinary diet the urine contains approximately equal amounts of four acids, namely HCl, H_2SO_4, H_3PO_4 and organic acids The acid reaction of the urine is due to the fact that two of these acids, namely phosphoric acid and organic acids, are less completely neutralized by base in the urine than they are in the body They therefore represent a saving of base to the body The two remaining urinary acids, HCl and H_2SO_4, because they are "strong" acids, that is, dissociate nearly all their hydrogen ions, cannot be present to any appreciable extent in a fluid of such relatively low [H] as urine These two acids must therefore carry their full equivalence of base into the urine, that is, they are excreted fully neutralized.

Renal Regulation of Total Base The kidney strives to maintain a constant total base concentration in the blood, it does not concern itself specifically with maintenance of the alkali reserve, that is, the fraction of total base which is combined with bicarbonate Constant total base is necessary because in view of the ready adjustability of bound CO_2 in accordance with the amount of base available, total base determines the total salt content of the plasma and therefore the osmotic pressure

Digestive "Alkaline Tide." Each food has a characteristic pattern of acids and bases, but any appreciable effect of these on the internal acid base balance is prevented by the great regulatory capacity of the kidneys. The urine becomes more than usually alkaline ("alkaline tide") about an hour after a meal especially after meals which stimulate marked secretion of gastric HCl This change does not occur in achlorhydria After gastric digestion is complete the chloride is reabsorbed in the intestine and the urine becomes more acid This late effect of one meal may obscure the alkaline tide from a second meal.

Renal Excretion of Ammonia In addition to excretory activities the kidney engages in at least one secretory process in order to assist in acid base regulation namely the formation of ammonia to combine with acid substances when there is excess acidity of the blood. It should be noted that increase of ammonia is found only in acid urine and is associated with acidosis not alkalosis Ammonia excretion plays an even more important part than the excretion of titratable acid in preserving and restoring the alkali reserve in acidosis Both the acid and

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bicarbonate, the CO content and the pH of the blood, excess of alkali has the opposite effects

Acidosis and Alkalosis Acidosis may be broadly defined as an abnormal condition caused by the accumulation in the body of an excess of acid or the loss from the body of alkali The more common cause is accumulation of acid the process is said to produce a state of acidosis when it causes either the bicarbonate of the blood to fall below or the hydrogen ion concentration to rise above the normal limits Alkalosis is an abnormal condition caused by the accumulation in the body of an excess of alkali or by the loss of acid Either process increases the bicarbonate and usually diminishes the [H] of the blood In both acidosis and alkalosis the general rule is that the bicarbonate content and the hydrogen ion concentration of the blood move in opposite directions However, this rule does not hold when carbonic acid is the substance at fault, that is, when the acidosis or alkalosis is due to an excess or deficiency of carbonic acid

Respiration is ordinarily regulated in accordance with metabolic production of CO_2 When other factors (such as voluntary control, oxygen lack morphine) exert a considerable influence upon respiratory activity, the CO_2 tension of the alveolar air and blood becomes abnormally high or low When overbreathing markedly diminishes the CO_2 tension, the resultant alkalinity may become so great that tetany develops In such a case, to raise the [H] toward the normal level, excretion of acids by the kidney ceases The acids so retained neutralize some of the bicarbonate of the blood, liberating CO_2, but usually this compensatory reduction in alkali is not great enough to bring the CO_2 tension or $[H^+]$ quite up to normal, that is, compensation is not complete Therefore this diminished alkaline reserve from acid retention can be distinguished from primary loss of alkali by simultaneous determination of the CO_2 tension or of the hydrogen ion concentration When the extraneous influences, that is, factors other than CO_2 tension the normal regulator, affect respiration so as to cause not a decrease but an increase in CO_2 tension and [H] an opposite response occurs, there is a compensatory retention of bicarbonate by the kidney with consequent restoration of the [H] nearly but not completely to normal

In any given case the hydrogen ion concentration may be high, low or normal and the bicarbonate content either high, low or normal. There are, therefore, nine possible combinations, but for clinical purposes the important conditions are related to alkali excess or deficit (metabolic types) and to CO_2 excess or deficit (respiratory types) A disturbance of alkali may be offset by a change in CO_2 and vice versa,

the basic side of the ionic structure of the body fluids, therefore, is protected by a substance which is widely adjustable in amount and also is volatile, namely carbon dioxide and ammonia, respectively.

DISORDERS OF ACID-BASE BALANCE

Significance of Plasma pH: The term blood pH always refers to the plasma pH, for there is no direct information concerning the pH in the interior of the corpuscles The physiological significance of plasma pH is twofold 1 It indicates the actual concentration of hydrogen and hydroxyl ions, in the blood and in the other body fluids which are influenced by the state of the blood Physiological processes are affected by the reaction of these fluids 2 It shows whether the respiratory apparatus is operating normally to prevent any considerable change of the H_2CO_3 $BHCO_3$ ratio in the blood

Range of pH and CO_2 Values in Health and Disease. Normal values for blood are as follows

pH—7 4 (venous blood only 0 02 or 0 03 lower)
CO_2 content—55 to 74 volumes per cent
CO_2 tension—37 to 58 millimeters Hg

Abnormal variations which occur are as follows

pH—7 0 to 7 8 (tetany is likely to appear when pH rises to the vicinity of 7 6)
CO_2 content—Minimum 4 volumes per cent (10 common, recovery may occur)
Maximum 123 volumes per cent in a case of pyloric obstruction has been reported, there was no tetany
CO_2 tension—Maximum 70 mm Hg (75 in venous blood) Concentrations of CO_2 as great as 40 per cent in air enriched with oxygen have been administered to patients over periods of three to five minutes without fatal results Far lower concentrations can induce intolerable subjective sensations and narcosis
Minimum 10 (15 in venous blood)

Etiologic Types of Acid-Base Disturbances There are two types of abnormal acid-base conditions (1) *the metabolic type,* in which the primary disturbance is in the balance between the alkali and the acids other than carbonic acid, and (2) *the respiratory type,* in which the primary disturbance is in the CO_2 tension of the blood The best quantitative measure of the metabolic type of acid-base disorders is the alkali reserve of the plasma Deficiency of alkali causes a fall in the

3 Renal excretion of free buffer acids and ammonia, replacing the lost bicarbonate and later restoring the acid base balance to normal

4 Removal of chloride from the blood, leaving sodium to protect bicarbonate which would otherwise be destroyed Part of the chloride is displaced into the tissues and part is excreted in the urine as NH_4Cl

5 Combustion of the retained acids if they are organic acids

Respiratory Types of Acid Base Disturbance *CO_2 excess* is the least common of the four types of acid base abnormalities Provisions for the excretion of CO_2 by the lungs are so much more generous than those for the absorption of oxygen that interference with gas exchange must ordinarily cause death from anoxia before CO_2 accumulation becomes dangerous (a) The rate at which CO_2 diffuses through animal membranes is 20 to 30 times as great as the rate at which oxygen diffuses Possibly this is why, in the alveoli, complete equilibrium between air and blood is approximated for CO_2 (40 mm Hg) but not for O_2, normal arterial oxygen being about 100 mm as compared with alveolar oxygen tension of 105 mm (b) Oxygen lack is a poorer respiratory stimulant than CO_2 excess (c) Poor CO_2 removal in one part of the lung can be offset by increased CO_2 removal in other parts, whereas deficient oxygenation in one part of the lung cannot be balanced by overoxygenation elsewhere because the blood can hold only a limited amount of oxygen No excess of CO_2 is found in pneumonia

In animals the effects of partial obstruction of the trachea on the CO_2 tension and content of the blood have been found to be quite similar to those caused by breathing air enriched with CO_2 It seems that such primary CO_2 excess results after a time in increase of the alkaline reserve The bicarbonate may in fact rise to levels found in primary alkali excess The only constant symptom due to primary CO_2 excess is hyperpnea Headache may occur The effects on the kidney are similar to those of the metabolic type of acidosis, namely diuresis, acid urine and ammonia excretion In chronic respiratory obstruction, no increase of base occurs instead there is decrease of serum chlorides, Cl probably being excreted in the urine

CO_2 deficit from over ventilation occurs in response to oxygen want, exposure to dry hot air fever, hot baths and encephalitis CO_2 tension and [H] are lowered and the alkali reserve gradually diminishes The chemical status of the blood may be quite indistinguishable from that of primary alkali deficit, except for the hydrion, which may be increased in the latter The most serious symptom is tetany, which occurs

so that there is no change in [H^+] If the change in [H^+] normally induced by the original disturbance is entirely corrected by the opposing process the condition is called "compensated" acidosis or alkalosis, if some change in [H^+] persists, the condition is said to be "uncompensated" Alkali deficit has a particular tendency to become uncompensated, that is, to lead to an abnormal (increased) hydrogen ion concentration Alkali excess and alkali deficit refer only to the concentrations of "available" alkali, i e , alkali combined with bicarbonate and other buffer acids Base present in neutral salts, such as Na in NaCl, is not part of the available alkali Changes in the total amount or concentration of all the basic elements are referred to as "base excess" and "base deficit" These are not constantly associated with disturbances of acid-base balance In fact "alkali excess" may accompany "base deficit," as for example in pyloric stenosis

Metabolic Types of Acid-Base Disturbance. *Alkali excess* may be produced by retention of alkali or by loss of acid The effects and symptoms are the same and do not indicate which factor is the cause in any given case Bicarbonate increases, [H^+] falls and tetany may occur Respiration is diminished and alveolar CO_2 tension is increased Decrease of acid excretion (including CO_2) and increase of alkali excretion are the chief factors in restoring normal acid-base balance

Alkali deficit may be caused by loss of alkali or by retention of acid, or both The chief blood changes are reduction of bicarbonate and CO_2 concentrations, and, in the more advanced stages, rise of hydrogen ion concentration The most constant symptoms are hyperpnea (increased depth rather than increased rate of breathing) and dehydration Subjective symptoms may not appear until the alkali reserve has fallen to half normal There is decreased alveolar CO_2 tension and the kidneys excrete more water, acid phosphates and ammonia One of the early effects is to wash out sodium and to a lesser extent potassium, calcium and magnesium from the body, these bases being required to neutralize the excess acid in the urine Only when the supply of these basic ions becomes low is ammonia excreted in large amount An amount of body water is excreted proportional to the amount of alkaline metals lost Diuresis and dehydration therefore are regularly associated with acidosis

The responses of the organism to alkali deficit caused by retention of non-volatile acids may be summarized thus

1 Neutralization by buffers
2 Respiratory lowering of the CO_2 content of the blood to or below the original level

CO_2 tension and hydration of the blood, it also increases the tolerance for CO_2 in the inspired air

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THE ALIMENTARY TRACT AND ACID BASE BALANCE

The influence of the alimentary canal upon acid base balance is ordinarily much less important than that of the kidney The alkalinity of the feces is chiefly due to the bivalent alkalis Ca and Mg, for which the gut is the chief channel of excretion The chief acids are carbonates, phosphates and fatty acids The stools ordinarily contain only small amounts of sodium, potassium, chloride and inorganic sulphate

The secretions and contents of the entire alimentary canal are approximately in osmotic equilibrium with the blood plasma (except during active digestion) and differ from the latter only in the details of their electrolyte patterns Loss of gastric secretion entails chiefly loss of chlorine ions Some Na is lost but the amount of Na equals that of Cl only in cases of complete anacidity The result of such depletion of the serum Cl is primary alkali excess with its usual sequellae

Pyloric Obstruction Pyloric obstruction results in loss of some Na but much more Cl, and of water The result is an increased alkali reserve, decreased plasma Cl and decreased [H], that is, primary alkali excess. The highest bicarbonate values have been observed in pyloric obstruction, the CO_2 content sometimes exceeding 110 vols per cent By way of compensation pulmonary ventilation diminishes, so that CO_2 is retained, tending to increase the CO_2 tension and therefore the hydrogen ion concentration Active tetany is rare, and perhaps occurs only when some increase in respiratory activity permits further fall in [H] Slight hyperpnea suffices to induce tetany in these cases, possibly because of some predisposing effect of hypochloremia

In pyloric obstruction ketone acids resulting from starvation often partly offset the bicarbonate increase produced by loss of chloride Accumulation of inorganic phosphate and sulphate, by serving to replace some of the lost Cl, may have the same effect. When gastric HCl concentration is low, the tendency to alkalosis from vomiting is correspondingly decreased

when the pH is about 7 6 The urine becomes alkaline, ammonia excretion ceases, diuresis occurs and there is slight ketonuria

ACID-BASE BALANCE IN VARIOUS CLINICAL CONDITIONS

Starvation Starvation causes the formation and partial retention of an excess amount of acids including acetoacetic and hydroxybutyric acid, but the alkali reserve seldom falls as much as 50 per cent below normal The acidosis is less severe than in diabetes because the carbohydrate derived from protein can be burned in simple starvation but not in diabetes With diets completely lacking carbohydrates (ketogenic) an alkali deficit quite as severe as that of complete starvation can be produced

Traumatic Shock In traumatic shock there is commonly reduction of the carbon dioxide and bicarbonate content of the blood This is probably not a primary CO_2 deficit, for the effective pulmonary ventilation usually does not seem to be greatly augmented, and tetany does not occur The change is probably due to anoxia

Severe Hemorrhage Severe hemorrhage is attended with lowering of bicarbonate and increased $[H^+]$, that is, primary alkali deficit This condition seems to be the result of excessive lactic acid production because of inadequate oxygenation of the tissues The acidosis of hemorrhage is of short duration Anemia of itself has no appreciable influence on the acid-base balance

Oxygen Want Oxygen want causes at first alkalosis by excess removal of CO_2, which becomes compensated by renal excretion of alkali If the oxygen want is extreme enough to interfere with combustion of carbohydrate the alkalosis is replaced by an intense acidosis due to accumulation of lactic acid Circulatory stasis causes increased CO_2 tension and hydrogen ion concentration, decreased bicarbonate and chloride, and increased concentration of the blood and serum protein

Ingested Salt The effect of ingested salt on the acid-base equilibrium depends on the ultimate fate of the individual ions of which the salt is composed The effect of an acidifying or alkalinizing salt on the internal acid-base balance is equal to the effect of an equivalent amount of the corresponding pure acid or of bicarbonate Acidifying salts cause diuresis

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In diarrhea proportionately more Na is lost than Cl, so that the serum Cl concentration is usually high, there is acidosis with bicarbonate deficit The latter is exaggerated in severe cases by coexistent deficiency of total base The best treatment for both the dehydration and the alkali deficit is normal salt solution, with the addition of glucose if starvation is a feature of the condition Bicarbonate seems to be of less importance Peters and Van Slyke state "If the deficiency of salt and water is remedied and a free urine flow established, the kidney seems to be quite capable of making finer adjustments among individual ions"

The dehydration resulting from vomiting naturally involves the excretion of an amount of base proportional to the total volume of water lost by all routes. This base is lost partly in the urine and partly as neutral salt in the vomitus itself. The urine therefore usually becomes alkaline, containing large amounts of bicarbonate and very little ammonia and chloride. Sometimes, when there is general base deficiency and a consequent effort to conserve base, the urine remains acid in spite of alkalemia. Administration of NaCl in such a case causes the urine to become alkaline.

Gastric fistula affects the acid-base balance in the same manner as pyloric obstruction

Taylor (1937) reports a case of fatal alkalosis believed to be induced by postoperative gastric suction following operation for perforated duodenal ulcer. However, serious alkalosis from this cause is very uncommon.

Intestinal Obstruction and Fistula Intestinal obstruction causes changes similar to those of pyloric obstruction The lower the obstruction the less acid is the fluid lost because of the relatively larger proportion of intestinal secretions, therefore the tendency to reduction of Cl and increase of CO_2 is less

Intestinal fistulae permit loss of alkaline intestinal secretions and therefore induce a primary alkali deficit

The secretions of the pancreas and the small intestine contain very little chloride and correspondingly larger amounts of bicarbonate The concentration of base (chiefly sodium) is approximately equal to that in the blood plasma Loss of these secretions therefore results mainly in loss of sodium bicarbonate, causing primary alkali deficit Loss of bile, which is alkaline, has a similar but smaller effect, for some of the sodium bicarbonate is replaced by bile salts When loss of gastrointestinal secretions is attended by vomiting or other factors interfering with the ingestion or absorption of food, starvation acidosis may modify the effects on the acid-base balance.

Vomiting and Acid-Base Balance Vomiting from whatever cause may disturb acid-base balance in four ways (1) Dehydration Dehydration probably cannot in itself produce acidosis (alkali deficit), unless it be that the resulting anuria interferes with renal excretion of ammonia and acid In this case an acidosis similar to that of nephritis might be expected. (2) Starvation acidosis (3) Loss of HCl (4) Loss of salt (electrolyte deficiency) The end result depends on which of these factors predominate Parenteral administration of an adequate amount of solution of NaCl and glucose mitigates all four factors

(2) Production or consumption of materials on the part of the living cells bathed by the fluid, or,

(3) Loss of materials to the external environment (excretion)

Restoration of the composition of the body fluid after alterations have occurred must be effected by one or more of these same processes The kidney can only excrete There may perhaps be minor exceptions to this statement but even the new formation of ammonia in the kidney is in reality a device for the excretion of acid The kidney excretes various substances with uncanny discretion and selectivity, and at times it is hard to understand why the kidney fails to excrete certain other substances It is not necessary, however, to conclude that one function of the kidney is to "prevent excretion" of a certain substance or substances any more than to ascribe a similar "excretion prevention" function to the liver or to other organs

The function of the kidney, as indicated above, is to preserve the chemical constitution of the interstitial body fluid (which is not the same as the blood) In order to do so it attends to the following characteristics and components of that fluid and regulates them by producing suitable alterations in the composition of the blood by means of excretion

(1) Total volume of interstitial body fluid
(2) Osmotic pressure
(3) Concentration of individual constituents
(4) Reaction
(5) Endogenous waste products
(6) Exogenous foreign substances

THE MECHANISM OF URINE FORMATION

The Glomeruli *Formation of Plasma Filtrate*, The glomerulus performs only the relatively simple function of filtering the blood so as to separate from it a fluid identical with plasma except for the removal of the plasma proteins The removal of the proteins from the plasma (or rather, the withdrawal of plasma from its proteins) is therefore the chief work done by the glomerulus Since the process is considered to be a purely mechanical filtration, the glomerulus is a more or less passive agent, the energy required for the process being derived from the *pressure* of the blood The pressure of the blood in the capillaries of the glomerulus is higher than that in any other capillary area in the body, being only about 20 per cent lower than the pressure in the carotid artery, that is about 100 to 110 millimeters Hg Part of this pressure is expended in overcoming the osmotic pressure of the plasma proteins,

Chapter XV

THE KIDNEY

THE FUNCTIONS OF THE KIDNEY

Relation of the Kidney to the Interstitial Fluid: The ultimate function of the kidney is to preserve the chemical constitution of the internal environment of the body The internal environment does not mean the blood, for in general the cells of the body do not live in direct contact with the blood Instead they are immersed in a lake of interstitial fluid which is a continuous body of liquid whose chemical composition is everywhere kept uniform by means of the constant circulation of the blood through it This interstitial fluid may be said to be bounded on one side by the living tissue cells of all kinds and on the other side by the blood stream The kidney is not concerned directly with the chemical state of affairs within the tissue cells, for the latter are in full charge of their own chemical interior and well able to maintain it themselves if their outer chemical environment, that is, the interstitial fluid, is suitable in composition What is called the internal environment of the body is thus the external environment of the tissue cells.

The kidney's function is to preserve the proper composition of this body of interstitial fluid, but the kidney is not in direct communication with the fluid itself, being separated from the latter by the blood It therefore can accomplish its purpose only through the mediation of the blood The composition of the blood reports the chemical status of the interstitial fluid to the kidney, the latter alters the blood only with a view to the consequent influence upon the interstitial fluid Changes in the blood wrought by the kidney, because they are more obvious and accessible to measurement than those in the interstitial fluid, tend to obscure the greater importance of the latter, similarly the chemical stimuli responsible for alterations in kidney function are commonly sought for in the blood, whereas the blood is only the agent transmitting stimuli really originating as changes in the composition of the interstitial fluid

The fluid medium of the body can suffer changes only by

(1) Accession of materials from the external environment, that is, by way of the alimentary tract and lungs chiefly,

and restore them to the blood so as to maintain the normal composition of the latter It is by means of this tubular activity that the first four of the functions of the kidney enumerated above are performed Tubular reabsorption of chloride differs from that of glucose in that the former is under variable external control (pituitary, adrenal cortex) whereas the latter is always maximal The tubules refrain from reabsorbing the no-threshold substances which include certain waste products of metabolism such as creatinine and urea and certain exogenous foreign substances, for instance, dyes and such toxins as lead (Some urea, however passes out of the tubules back into the blood by a process of passive diffusion) The excretion of the no-threshold substances, which embraces the fifth and sixth functions of the kidney enumerated above, is therefore largely dependent on the activity of the glomeruli However, a few exceptional no-threshold substances are eliminated not only by glomerular filtration but also by active excretion by the tubule cells from the blood into the lumen of the tubule (e g creatinine, phenol red)

The action of the tubules with regard to the different constituents of the blood is highly selective, for no two substances are treated exactly alike or are concentrated during their excretion to just the same degree Moreover, any given substance may be reabsorbed by the tubule at one time and not reabsorbed at another time, according as the needs of the body vary The mechanisms which regulate these complex variations in the activities of the tubules are unknown, because the chemical processes which occur within the cells of the tubules must be extremely delicate and complex, the term "vital activity" has been used in reference to them

New Formation of Ammonia and Hippuric Acid One substance, ammonia, is manufactured by the tubule cells and excreted in the urine, though some of it passes into the general circulation by way of the renal vein Aside from this absorbed fraction of ammonia the kidney is not known to produce any internal secretion, that is, any substance which it manufactures itself and secretes into the blood stream Hippuric acid is the only other substance known to be new-formed in the cells of the renal tubules, it is excreted in the urine An enzyme (phosphatase) capable of splitting organic phosphate has been found in the kidney and may possibly be responsible for producing part of the inorganic phosphate eliminated in the urine

In summary the formation of urine is accomplished as follows The glomerulus forms a simple colloid free (protein free) ultrafiltrate of blood plasma From this substrate the tubules remove water and certain

this osmotic pressure has been found to be about 40 millimeters Hg and represents the tenacity with which the proteins try to hold the fluid in which they are contained and hence the resistance to be overcome in separating them The remainder of the blood pressure, about 60 to 70 millimeters Hg, is the net or effective filtration pressure Back pressure in the ureter does not check the flow of urine completely until the back pressure equals the net filtration pressure Filtration ceases entirely when the general arterial blood pressure falls to about 40 millimeters Hg because then the glomerular capillary blood pressure is nullified by the osmotic "pull" of the plasma proteins.

Besides the necessity for an adequate blood pressure, a sufficient *volume* of blood must flow through the kidney per unit of time if glomerular filtration is to proceed Even when the pressure is high the blood flow may conceivably be diminished to zero, as for instance by closure of the glomerular efferent vessels, under these circumstances the small amount of blood contained within the glomeruli at the time would quickly be filtered and then urine formation would cease entirely

The glomeruli are not continuously active, for a given glomerulus may remain practically bloodless for considerable periods, or the blood may at times flow through only a part of the capillary tuft The degree of circulatory activity in the glomeruli, which is apparently under vasomotor control, determines the total filtering area of the kidney and therefore influences directly the rate of formation of glomerular fluid Because of the peculiar arrangement of the circulation in the kidney the capillary pressure and the blood flow in the glomeruli can be regulated more sensitively than in other tissues In other tissues, arteriolar vasoconstriction invariably diminishes the blood pressure in the capillaries, whereas in the glomeruli the effect on capillary pressure will depend on whether the arteriolar constriction is exerted upon the afferent or upon the efferent arteriole

The Tubules *Reabsorption from the Glomerular Filtrate* The tubules perform all the more complicated functions of the kidney They do so almost entirely by reabsorbing from the glomerular filtrate varying amounts of the many different substances which it contains These substances fall into two classes, those which the kidney tries to eliminate from the blood entirely and excretes as long as a trace of them remains (no-threshold substances) and those which the kidney tries to maintain at a certain concentration in the blood and excretes only when they are present in higher concentration (threshold substances)

The tubules reabsorb from the fluid within their lumen the threshold substances, such as water, chloride and glucose, in varying proportions

of the interstitial fluid of the body The glomerular filtrate is perhaps a quite exact specimen of the general interstitial fluid since it bears a similar relation to the blood as the latter, that is, it is formed from the blood by simple filtration across a capillary membrane

Excretion of Basic Radicals When the concentration of bicarbonate in the serum is increased, whether because of the actual administration of large amounts of bicarbonate or the relative increase of bicarbonate which occurs when chloride is lost by vomiting as in pyloric obstruction, the urinary excretion of bicarbonate is augmented In the case of vomiting renal excretion of chloride is reduced, as would be expected If the vomiting continues for some time the reduction of serum chloride and increase of serum bicarbonate become aggravated, correspondingly, the urinary excretion of chloride remains low, but the behavior of bicarbonate is less simple and consistent, for at a certain point the augmented excretion of bicarbonate ceases, and even though the serum bicarbonate is still excessive, the concentration of bicarbonate in the urine decreases markedly and may become negligible, the urine even becoming acid in reaction

This retention of base in spite of an excess concentration of base in the serum is referable to the base supplies of the body as a whole. Up to a certain point the kidney is ruled by the acid radical, that is, by the excess of bicarbonate in the serum, and strives, by excretion of bicarbonate to restore the balance between bicarbonate and chloride in order to reestablish the normal *pattern of acids* in the serum The bicarbonate can be removed only in combination with an equivalent amount of base (sodium), so that after the kidney has acted in response to the excess serum bicarbonate for some time, it has incidentally excreted a quantity of valuable *sodium*

When the supply of sodium in the body has been depleted to a certain degree, the kidney is made aware of this fact by a tendency toward a decrease in concentration of sodium in the serum. Heeding this signal, the kidney refuses to permit further loss of sodium, therefore it must suspend excretion of bicarbonate regardless of the excessive concentration of the latter in the serum Between the two evils, relative excess serum bicarbonate over chloride (with alkalosis), versus depletion of body sodium below a certain value, it chooses the former and permits the sodium supply to dominate the excretion of bicarbonate Presumably protective adjustments of kidney activities of this kind are accomplished chiefly by the selective reabsorption on the part of the tubules, but the intimate controlling factors are unknown

When the total volume of fluid in the body is diminished by profuse

solutes by reabsorption and to it they contribute a certain very few solutes by secretory activity

RENAL EXCRETION OF WATER AND ELECTROLYTES

Control of Volume of Body Fluids· Serum (or blood) volume is maintained by a balance between renal activity on the one hand and the fluid exchange between the capillaries and the interstitial spaces on the other Constancy of the total volume of blood is a matter of importance, constancy of the total volume of the interstitial fluid, which may be pictured as bounding the blood on one side, is relatively unimportant, and the same is true of the urine volume, which is formed at the opposite side of the blood Since the blood is thus provided with a variable reservoir on one aspect and a controllable outlet on the other aspect, it is apparent that suitable conditions for continuous maintenance of the proper blood volume are provided Within limits, changes in the volume of fluid in the interstitial reservoir do not of themselves induce reactions on the part of the kidney, it is only when these changes affect the volume of the circulating blood that the kidney is apprised of the dislocation of the body fluid volume, and then it responds accordingly

The kidney is rather indifferent to changes in the *volume* of the general body fluids up to the point at which these changes are reflected by corresponding disturbances in blood volume Hence it is that even in a normal individual the kidneys will permit edema formation when large amounts of physiological saline solution are administered rather rapidly The kidney offers less resistance to expansion of the volume of body fluid than to its contraction

Control of Composition of Body Fluids: A change in the *composition* of the interstitial fluid, as contrasted with a change in its total volume, has on the contrary a much more potent influence upon the kidney, for the kidney is immediately made aware of the chemical alteration in the interstitial fluid, the change is readily transmitted by diffusion to the circulating blood and is quickly reported by the latter to the kidney The blood serves as it were as a sample of the interstitial fluid which the kidney "tests", if the sample is normal in quality, the kidney has no way of knowing from it how much fluid is in the reservoir from which it is obtained, but if the sample deviates *qualitatively* from the normal in any respect, the kidney is immediately aware of a like alteration in composition of the entire body of interstitial fluid It is reasonable therefore for the kidney to be more consistently sensitive to disturbances of chemical composition than to changes of total volume

Excretion of Acid Radicals Among the acid radicals the electrolyte pattern of the serum is much less fixed than among the bases It is evident that some group of ions must be subject to considerable variability under the influences of varying diet and activity, and the acids rather than the bases bear the brunt of these vicissitudes of intake and function Within wide limits the two chief acid ions, chloride and bicarbonate, are interchangeable For example, in loss of chloride (but not sodium) by vomiting in pyloric obstruction, very marked alkalemia would immediately result were it not for the fact that the sodium set free in the serum promptly joins with ever present carbon dioxide to form sodium bicarbonate, the subsequent elimination of the latter in the urine mitigates the alkalosis considerably This compensatory disposal of sodium proceeds until the body decides it can spare no more of such a valuable ion, and refuses to allow further loss regardless of alkalosis It is noteworthy that carbon dioxide, which the kidney excretes in place of chloride in defense against alkalosis, is an endogenuos product constantly available because it is continuously formed by the combustion of food stuffs in all living tissues, and that ammonia, which the kidney excretes in place of sodium in defense against acidosis, is likewise an endogenous product formed in the kidney from urea In either case an "inexpensive" waste product is substituted for the valuable chloride or sodium ion, and is excreted by the kidney in place of the latter It seems that the stimulus which incites the kidney to perform these conservative operations is the relative proportions of the various cations and anions impinging upon it, rather than the coincident alteration in the pH of the body fluids Disturbances of pH evoke respiratory responses but apparently have no special domination over the kidney, as mentioned above, despite a markedly alkaline state of the blood in the late stages of pyloric stenosis, the kidney excretes acid urine for the preservation of sodium and in disregard of pH

Water Diuresis When a huge amount of water is ingested, it is practically completely eliminated by the kidneys in the succeeding few hours The glomeruli produce the same volume of filtrate as normally, but the tubules reabsorb less water than before, probably because of inhibition of the antidiuretic action of the postuitary gland. Probably the stimulus which causes these changes in activity or which "notifies" the kidney and the postuitary of the needs of the moment, is the more dilute state of the blood resulting from the absorbed water However, these organs must be enormously sensitive to the altered concentration of the blood, since the degree of dilution of the blood resulting from administration of even tremendous amounts of water is barely measurable For ex

sweating, diarrhea or other dehydrating processes, the kidney eliminates solutes in proportion to the amount of water lost, so that the total concentration of electrolytes in the serum is preserved or restored. Though the total concentration of electrolytes is more zealously guarded than the concentration of the individual ions, the normal inorganic chemical pattern is preserved in many details. For example, in pyloric obstruction with loss of chloride, the remaining excess sodium is excreted by the kidney in combination with bicarbonate as mentioned above; as a result the total concentration of electrolytes in the body fluid remains unaltered and also the normal proportion of the various ions is preserved. The total *amount* of electrolytes in the body is diminished, but there is a corresponding diminution in the total volume of body water.

Total Electrolyte Concentration. The total concentration of electrolytes in the serum is more rigidly protected than either the total osmotic pressure or the colloid osmotic pressure. Exogenous salt is excreted with the greatest possible economy of endogenous water, and exogenous water is eliminated with the utmost economy of endogenous salt. The total electrolyte concentration is determined fundamentally by the total base (principally sodium), for the concentration of acid radicals (principally chloride and bicarbonate) parallels the supply of base. In its adjustment of the total electrolyte concentration the kidney preserves also the normal electrolyte pattern, with especial emphasis on total base (the chief item of which is sodium), for the individual bases are not interchangeable to any appreciable extent. For example, in depletion of sodium, sodium salts are largely retained by way of compensation; there is no tendency to retain potassium salts even as a temporary substitute. Such substitution could hardly be very effective in any event, since potassium constitutes less than 4 per cent of the base in serum whereas sodium constitutes more than 90 per cent. There is likewise no detectable tendency for sodium to reciprocate with calcium or magnesium.

In summary, the kidney, being solicitous chiefly about the *total electrolyte* concentration must pay particular attention to maintaining *total base* concentration, since so much of the acid content of the blood consists of the volatile substance CO_2 which requires base in order to remain in the blood. Since the total base is composed chiefly of *sodium*, and for some reason other basic radicals cannot be substituted for it, the sodium ion content of the body appears to be especially protected by the kidney and to have therefore a particular influence in determining how much *water* may be excreted.

probably due to inability of the kidney to discover the extent of the fluid stores by any direct means That it eventually becomes aware of and concerned about any excess, however, is shown by the fact that it ultimately eliminates administered normal salt solution

Both water and salt solutions cause a more marked diuresis when administered by vein than when given by mouth or by rectum The fluid is retained in the body longer in the latter cases and (since the blood is not diluted more) this must be due to some factor facilitating passage of the absorbed fluid from the vessels into the tissues, or encouraging its retention in the latter This factor is unknown

It has been suggested that fluid absorbed across a mucous membrane receives from the latter during the process some substance or substances which assist in the retention of the fluid It is likely that fluid injected directly into a vein is never as delicately adjusted to chemical conformity with the blood and tissues as fluid which is first exposed to, and accepted into the body at the discretion of, a living mucous membrane

When practicable, therefore, administration of fluid by way of the alimentary canal is generally preferable to intravenous injection of an equal amount. Unlike fluid injected parenterally, fluid absorbed from the intestine is perhaps "processed" in some manner in the liver, for this organ is interposed between the site of absorption and the general interstitial fluid of the body

Diuresis produced by drugs is in practically all cases referable to diminished reabsorption of water and solutes in the tubules

RENAL REGULATION OF ACID BASE BALANCE

The manner in which the kidney takes part in maintaining the acid base balance of the body is described previously The chief factor is the excretion of varying relative amounts of *acid and basic phosphate* An accessory factor is the new formation of *ammonia* from urea by the kidney, the ammonia is combined with acids, which are thus eliminated without carrying with them the sodium or other fixed base which would otherwise have to be lost from the body

Alkali Therapy and Urinary Stone _ As pointed out by Eisele, the usual medical treatment of peptic ulcer produces conditions favorable to the formation of urinary stones namely, an increase in the urinary solids, a high specific gravity of the urine, the excretion of large amounts of crystalloids and a shift of the pH of the urine to the alkaline side Eisele found in a group of 505 patients with urinary stone, that 43 (8 5 per cent) had had ulcer treatment before symptoms of stone appeared, and 13 (2 6 per cent) had been subject to gastrointestinal

ample, when five liters of water are drunk in a period of two hours, the hemoglobin concentration of the blood decreases by less than 2 per cent Most of the water is apparently sequestered in the tissue spaces at once, and then returned to the blood only as fast as the kidneys can eliminate it

The total amount of solids eliminated during a period of water diuresis is approximately the same as in an equal period of complete abstinence from fluid This is one example of the general truth that in their excretion the urinary constituents (including water) are largely though not entirely independent of one another

Sodium Chloride Excretion Isotonic saline solution taken by mouth is not as quickly eliminated as water It causes only a slight diuresis, but one which lasts over a considerable number of hours (24 or more) depending upon the amount ingested This result is obtained even though the blood may be diluted to the extent of a decrease of 10 per cent in the hemoglobin concentration, in such a case the total osmotic pressure of the blood is of course not altered appreciably The administration of normal saline provokes the kidneys to practically no extra activity because it does not appreciably alter the chemical composition of the serum, despite the dilution of the cellular elements and colloids

Hypertonic salt solution produces the same effect as isotonic solution but the diuresis it excites is even less marked and more prolonged than in the case of isotonic saline

In both cases the dissolved salt, which can readily permeate the tissues, becomes dispersed in the intercellular fluid together with an amount of water sufficient to establish approximately normal osmotic pressure relations, the excess salt is then eliminated rather leisurely and with it, necessarily, a proportional amount of water

Normal sodium chloride solution is only gradually excreted, as mentioned above It might be supposed that the delay in its excretion is to be attributed to its isotonicity, since an equal volume of hypotonic sodium chloride or pure water will provoke diuresis It is more correct however to ascribe the slow excretion of normal saline, not to its isotonicity as such, but to the fact that it produces a minimal alteration of the chemical composition of the serum For an isotonic solution of potassium chloride is excreted as fast as pure water It is apparent that the total volume of fluid in the body is of less interest to the kidney than the composition of the fluid, equal amounts of NaCl and KCl alter the volume of body fluid to the same extent, yet they elicit different reactions on the part of the kidney.

As suggested above, this relative indifference to total volume is

polyuria has been checked by pituitary administration, he develops symptoms attributed to "water intoxication," such as headache, nausea asthenia, incoordination, convulsions and coma

In animals fatal water intoxication can be induced by the injection by stomach tube of very large amounts of water, death being preceded by coma and convulsions The "toxic" effects of excess water in man and animals are ascribed to increased intracranial pressure induced by edema of the brain, the edema is said to be particularly marked around the blood vessels Certain manifestations of uremia are believed to have a similar explanation

Theoretically it would seem possible for the reverse condition, namely an excessive secretion of the postuitary antidiuretic hormone to occur clinically in disease Grassheim has reported a case of primary oliguria in which a cystic tumor in the midbrain was found at operation The condition was relieved following the operation and the contents of the cyst when injected into dogs had an antidiuretic effect.

Adrenal Cortex Adrenalectomy induces diuresis and depletion of salt affecting only sodium, chloride and bicarbonate, but not potassium or phosphate These effects are due to the loss of adrenal cortical substance and are apparently brought about by a lessening of the power of the tubules to reabsorb sodium salts and, to a lesser extent, water

Thyroid The thyroid increases urine production somewhat

RENAL FUNCTION TESTS

Urea Clearance Test The most exact and most sensitive test of renal function available is the *blood urea clearance test* The test consists of determining the total amount of urea excreted in the urine in a given period of time and then, by reference to the concentration of urea in the blood at the time, determining what volume of blood would have to give up all its urea to yield the amount excreted For example, if during one minute 3 cubic centimeters of urine is excreted containing 10 milligrams urea per cubic centimeter, the urine volume (*designated* by V) multiplied by the urine urea concentration (designated by U) gives the total amount of urea excreted during the minutes = 30 milligrams If at the time, each cubic centimeter of blood contained 0.3 milligram urea (this blood urea concentration being designated by B), then the number of cubic centimeters of blood that would have to give up all their urea to yield the 30 milligrams actually recovered is

$\frac{30}{0.3}$ = 100 cubic centimeters This is the so-called urea clearance

distress and had taken alkalis habitually Hence in 11 1 per cent of all the patients with lithiasis, alkali ingestion possibly played a rôle

CONTROL OF KIDNEY FUNCTION

Nervous Control of Kidney Function: The kidney receives a sympathetic nerve supply derived from the sixth to twelfth thoracic segments of the spinal cord having its cell-station in the renal ganglion in the hilum of the kidney The nerves probably influence urine formation only by virtue of their action upon the blood supply of the kidney, and not by any direct secretory effect There is apparently no active parasympathetic supply, though vagus fibers can be traced to the kidney, these perhaps are afferent in function Denervation of the kidney results in the formation of an increased amount of urine of lessened specific gravity The afferent nerve fibers from the kidney enter the spinal cord by way of the two lowest thoracic and the first lumbar posterior nerve roots in the dog according to White, who states that all signs of discomfort induced by distention of the renal pelvis were abolished when these nerve roots were severed

Hormone Control of Kidney Function. The kidney is subject to hormone control An excised perfused kidney functions in a distinctly different manner from the normal kidney or the intact but denervated kidney The incapacity of such an isolated kidney as compared to a denervated kidney within the body indicates hormone influences upon the latter

Postuitary Postuitary hormone appears to augment the power of the kidney to reabsorb water in the tubules, by a direct action on the latter It has, therefore, an antidiuretic action, diminishing the output of urine Its action is not that of a general renal depressant, however, for the smaller amount of urine excreted contains an increased total amount of chloride, and the oxygen consumption of the kidney is increased In that it causes the tubules to reabsorb more water than they otherwise would, postuitary hormone may be regarded as a renal stimulant, the performance of this added work, done against osmotic resistance, requires the greater oxygen utilization observed

The hormone produces no appreciable effect whatever upon the urine when administered to a normal resting individual, its action becomes manifest only when water has been given, in which case the hormone prevents or delays the diuresis which would otherwise result

In diabetes insipidus the blood serum is normal in composition in spite of the great amounts of fluid excreted If a patient with diabetes insipidus continues to drink excessive quantities of water after his

obtained by centrifuging in a standard manner, is examined unstained on the ordinary blood counting chamber, separate counts being made of the red blood cells, white and epithelial cells combined, and casts The normal upper limits of excretion of these formed elements for a 12 hour period are

Red Blood Cells	500 000
White and Epithelial Cells	1 000 000
Casts	5 000

RENAL INSUFFICIENCY

Absolute Renal Insufficiency Renal insufficiency may be absolute or relative Absolute renal insufficiency consists of the occurrence of azotemia in spite of basal protein catabolism and the presence of polyuria. Given the latter two conditions, an increased blood urea content suffices for the diagnosis Accumulation of urea in the blood may occur in the absence of renal disease in such conditions as high intestinal obstruction, fever with increased protein catabolism, absorption of inflammatory exudates and urinary obstruction, but in these instances there is either excess protein destruction or absence of polyuria

Relative Renal Insufficiency Relative renal insufficiency is the inability to excrete concentrated urine, azotemia being prevented by compensatory polyuria This condition may easily lead to absolute renal insufficiency if there occurs an increased intake or destruction of protein or a decrease of urine volume for any reason, such as lessened water intake or extrarenal loss of fluid, e g , by sweating, vomiting or diarrhea Relative renal insufficiency, which of course varies in degree, can be detected by various types of concentration tests Limitation of concentrating power is the most consistent sign of renal insufficiency from whatever cause

If both kidneys are removed or both ureters obstructed, uremia develops, characterized by loss of appetite, weakness, apathy and stupor, terminating in death in about a week. There is a marked increase in the nitrogenous constituents of the blood but there is no elevation of blood pressure and there are no convulsions It seems that hypertension and convulsions, though they occur with uremia, are not directly attributable to renal insufficiency If three quarters of the renal tissue is removed recovery may occur but if thereafter much protein is ingested, nitrogen retention polyuria and other evidences of renal insufficiency may result. After removal of one kidney there is only a temporary increase in the non protein nitrogen of the blood. It has been mentioned above that

It should be noted that it is expressed in terms of a volume of blood If

V = the volume of urine per minute
U = the concentration of urea in the urine, and
B = the concentration of urea in the blood,

then

$$\frac{UV}{B} = \text{the urea clearance}$$

This may be defined as the volume of blood from which all the urea would have to be removed in order to yield the amount of urea excreted in the urine in one minute In actual fact, of course, the urea excreted is not obtained by the complete removal of urea from just this volume of blood, but rather by the partial removal of urea from some larger volume of blood passing through the kidneys As the test is usually performed, the urine is collected for two consecutive equal periods, the total urine volume (V) of each specimen being measured and the urea concentration (U) determined The collection of the urine is best done by catheter to insure complete emptying of the bladder, in which case short periods of 15 to 20 minutes may be used If this is not feasible, spontaneous voidings may be used but the collection period should be at least one hour for each specimen Venous blood is collected at the time of collection of the first specimen (midpoint between the two periods) and examined for its urea concentration (B) The calculation $\frac{UV}{B}$ is made on the basis of one minute's excretion

The normal range of urea clearance is 60 cubic centimeters to 95 cubic centimeters, average 75 cubic centimeters The urea clearance is roughly proportional to the mass of active renal tissue, like basal metabolism, it is more closely correlated with the surface area of the body than with body weight The urea clearance is most reliable when urine flow is above 2 cubic centimeters per minute

As a guide to loss of renal function, determinations of the blood content of urea, creatinine and non-protein nitrogen are valueless by themselves, for it has been shown by means of the urea clearance test that about 60 per cent of renal function may be lost before the blood chemical findings become significantly abnormal

Urinary Sediment Count: The Sediment Count introduced by Addis is a semi-quantitative count of the various formed elements excreted in the urine in a given period of time, usually 12 hours The sediment,

tural lesions is notoriously unsatisfactory but an appropriate schematic correlation is indicated by the following table

TABLE XXIV

CORRELATION OF STRUCTURAL LESIONS AND FUNCTIONAL CHANGES OF THE KIDNEY

Type of Nephropathy	*Localization of Lesion*	*Pathology*	*Most Prominent Clinical Sign*
Glomerulonephritis	Glomeruli	Inflammation	Hematuria
Nephrosis	Tubules	Degeneration	Edema Albuminuria
Nephrosclerosis	Arterioles	Sclerosis	Hypertension

glomerular activity is normally intermittent, renal activity being very rarely maximal Hence it is that 50 per cent of the normal kidney substance can, by working twice as continuously, do the work usually performed by the total renal mass Accurate measurements of excretory ability can be made only if the kidneys are stimulated to unusual or maximal activity

Renal Ischemia and Hypertension *Renal Pressor Substance* Bilateral renal ischemia causes the development of hypertension. The ischemia causes the liberation of a pressor chemical substance ("renin") which is distributed by the blood stream and acts directly on the minute blood vessels throughout the body, inducing vasoconstriction In bilateral kidney diseases of various kinds this is probably the mechanism responsible for any resultant hypertension, at least in the majority of cases

Barker and Walters and also others have reported cases of hypertension with unilateral chronic atrophic pyelonephritis in which, following nephrectomy, the blood pressure returned to and remained at normal levels In many instances it appeared that the diseased kidney, which regularly showed arterial obstruction due to sclerosis, was the chief factor in the production of the hypertension

Renal Antipressor Substance That kidney extracts contain a pressor substance ("renin") has been known for some time The fact that this pressor substance induces a greater rise in blood pressure in nephrectomized than in normal animals led to the suggestion that normal renal tissue possibly forms some opposing substance having the property of limiting the effect of the pressor substance Some evidence that renal extracts can produce such an antipressor effect in hypertension has been obtained by Grollman, *et al*

In an animal with unilateral renal ischemia, removal of the normal kidney is followed by a marked rise in blood pressure This supports the hypothesis of the elaboration of an antipressor principle by the normal kidney The degree of renal hypertension seems to be dependent on the ratio of ischemic to normal kidney tissue Hypertensive pregnant animals commonly develop a well marked decline in blood pressure during the last part of pregnancy, probably because the fetus or the placenta forms some antipressor substance, following delivery, the blood pressure increases to its previous elevated level

Abeshouse reports 16 cases of hypertension associated with unilateral renal disease and reviews the literature on this subject

Correlation of functional changes of the kidney in disease with struc-

justified Certainly the anatomical proximity of the medulla to the cortex seems to be the only reason for considering these two portions as being a part of one gland In support of this idea, Cameron states, "There is no evidence to prove that the approximation in mammals is not fortuitous "

Because of this anatomical proximity, adrenal tumors, whether they be of the medulla or the cortex, give rise to certain similar physical

TABLE XXV

COMPARATIVE TABLE SHOWING DIFFERENCES IN MANY PHASES BETWEEN THE ADRENAL MEDULLA AND THE ADRENAL CORTEX

Characteristic	*Adrenal Medulla*	*Adrenal Cortex*
Embryological Origin	Ectodermal phaeochromoblasts in developing sympathetic ganglia.	Mesothelium of genital ridge.
Histological Appearance	Mass of polyhedral chromaffin cells.	Three distinct layers.
Physiological Activity	Produces Epinephrine.	Produces hormones for metabolism sex etc.
Effect of Blood Supply	Immediate necrosis following loss of blood supply Tissue cannot be transplanted	Tissue can be transplanted
Effect of Nerve Supply	Activity controlled by nerve action chiefly Ceases to function following denervation	Not controlled by nerves.
Results of Hypofunction	No specific insufficiency entity	Acute Waterhouse Friedrickson and Adrenal Apoplexy Chronic Addison's Disease, etc.
Results of Hyperfunction	Paroxysmal hypertension.	Adrenogenital syndrome etc.
Pituitary Control	No	Yes

changes Therefore, to avoid repetition when considering the medulla and the cortex separately, methods by which a tumor of this region may be demonstrated will be discussed at this time A certain number of tumors of the adrenal medulla or cortex may be palpated, and must be considered in the differential diagnosis of any tumor of the abdomen regardless of size or location In 1921, Cardelli developed a technique for the radiographic visualization of the kidney outline by the injection of air into the perirenal spaces This method did not receive popular

Chapter XVI

THE ENDOCRINE GLANDS

THE ADRENAL GLANDS

At the present time, great progress is being made toward better understanding of the normal and abnormal activities of the adrenal gland There remain, however, many problems to be explored and further information to be sought Endless research by tireless workers has now elevated the adrenal glands to a position of paramount importance Their proper function is recognized as being essential not only to good health but to life itself

Early descriptions of the adrenal or suprarenal gland resulted in misconceptions that persisted for many years Thomas Bartholenus in the 17th century described the adrenals as round bodies, located adjacent to but distinct from the upper poles of the kidneys These bodies, supposedly, contained a cavity, but no ducts This central cavity was filled with a dark viscid material which was felt to be one of the humors of the body, and was called "black bile " At that time postmortem examinations were somewhat ostracized, leaving many obstacles to be overcome before such an examination could be carried out, which usually resulted in a considerable delay after death had taken place We now know that soon after death, certain changes take place in the medullary portion of the adrenal gland An early postmortem autolysis results in disintegration and liquefaction of the central portion of the gland so that the black viscid material confined within the shell of cortex was thought to be a normal phenomenon This conception existed for almost 200 years

Though realizing that sharp criticism may be forthcoming, the author feels that the adrenal medulla and the adrenal cortex should be considered as two separate and distinct organs and, therefore, makes such a distinction in this presentation, with the hopes that it will give rise to better understanding and clearer insight into a subject which at the present time is undergoing metamorphosis When one considers the great differences between the adrenal cortex and the adrenal medulla (see Table XXV) as to embryological origin, histological structure, physiological activity, and pathological changes, such a division appears

for the additional work required of the heart during the period of elevated blood pressure The arterioles of the lung are relatively insensitive to the adrenalin It has long been shown that the adrenal gland in the resting stage could be treated with acid and granules made visible When the gland is stimulated to activity, these granules are seen to be extruded into the vein, giving a clear picture of its internal secretion Considerable evidence indicates that the adrenal medulla continuously secretes adrenalin and that the amount varies with the amount of stimulation Emotional excitement such as fear, anger, pain, effort and other such conditions, give rise to definite stimulation through the splanchnic nerves with resultant increased adrenalin output However, very minimal stimulation is necessary to cause a small amount of secretion Even the slight muscular exercise of walking slowly causes some output of adrenalin As has been intimated previously, removal of the adrenal medulla, denervation of this structure or complete sympathectomy does not disturb the normal body physiology to any real extent, and it is considered that survival minus the benefits of the adrenal medulla is possible It would seem that the normal physiological activity of the adrenal medulla is to liberate adrenalin quickly when certain stimuli arrive, and by so doing, allow a quicker response on the part of the body as a whole However, its lack or absence is not necessarily detrimental to life itself It would seem worthwhile to mention the work of Denber who infers that recurrent hypertension following operation, such as sympathectomy or splanchnectomy, is not due to regeneration of the nerve He feels that the return of hypertensive levels of blood pressure following such operations cannot be explained by regeneration of nerve fibers to the adrenal medulla

Hypofunction Since it has been brought out that under ordinary circumstances removal or complete denervation of the adrenal medulla does not necessarily alter the physiology of an individual, particularly when not subjected to stress and strain, there seems to be no specific clinical entity of adrenal medullary insufficiency It does not seem reasonable to even suggest that the manifestation of surgical shock, asthma angioneurotic edema, and other allergic processes, are in any way due to an insufficient activity of the adrenal medulla, even though the product of medullary activity frequently is used to alleviate these conditions

Hyperfunction Even though this subject is not one of pathological changes occurring in the adrenal medulla but rather deals with functional alteration a brief classification of tumors of this structure would seem feasible There are four general tumors of the adrenal medulla.

attention, however, until 1935, when Cahill pointed out advantages and tended to make the method more popular

The use of perirenal air insufflation is not without its dangers and today it is being used less frequently Kaplan and Green have recently made a survey based on the study of 72 excretory urograms made in cases in which the clinical pictures suggested the presence of a tumor of the suprarenal gland Bilateral surgical exploration of the suprarenal gland was subsequently performed in each case They considered that downward displacement of the kidney and the presence of a soft tissue mass in the suprarenal region were the two important urographic findings when attempting to confirm a tentative diagnosis of a tumor of the suprarenal gland Of the 72 cases they felt that the excretory urograms were of value in demonstrating the presence of a tumor in 29 of 39 cases in which tumors were subsequently removed In 10 of the 39 in which a tumor of the suprarenal was later discovered, excretory urograms failed to reveal any abnormality They found that there were two cases in which urographic findings indicated the presence of a suprarenal tumor, but none was found at operation They emphasize that the intravenous pyelograms seem to have value as a screening procedure in cases where the clinical picture suggests the presence of a tumor of the suprarenal gland

ADRENAL MEDULLA

The medulla is the central portion of the adrenal gland which on cut section has a grayish appearance Embryologically, the medulla arises from ectodermal phaeochromoblasts in conjunction with sympathetic ganglia, and must be considered to be of nerve origin It is composed of large polyhedral cells, the granules of which stain with chromic acid, hence the term, "chromaffin" Nervous control is chiefly through the splanchnic nerves which penetrate the cortex without innervating it and end in close relationship with the cells of the medulla Stimulation of the splanchnic nerves result in an increased output of adrenalin, on the other hand, interruption of the splanchnic nerve diminishes this output The blood supply derived from branches of the aorta, phrenic and renal arteries is essential, because once the blood supply to the medulla is cut off, there is necrosis, and only by maintaining a vascular pedicle could the medulla be moved to another location

Physiology The adrenal medulla produces a substance, adrenalin or epinephrine, which has a marked pressor effect by causing constriction of the arteries of the body This, however, excludes the coronary vessels which are dilated by its action, thus providing increased oxygen

A Symptomatic

1 *Typical Episodic Hypertension* This is the type in which relief from symptoms follows the diagnosis and surgical removal of a phaeochromocytoma

2 *Chronic Progressive Hypertension* In this type the condition remains unrecognized with progression of hypertension and usually the diagnosis of phaeochromocytoma is made at autopsy *

3 *Mildly Symptomatic* This type has chronic complaints over a long period of time A tumor may or may not be palpable The patients do not tolerate spinal anesthetics Severe hypertension has not yet developed There may be an alarming drop in blood pressure following an initial rise, but the patient will usually survive

B Asymptomatic

1 *Hypertension Incited by Stimulus* In this category the patient has no symptoms indicative of hypertension Blood pressure may remain normal. In their particular cases the blood pressure following a spinal anesthetic became extremely high followed by a sudden drop Their patient died and a diagnosis of phaeochromocytoma was obtained at autopsy

The author's interest in phaeochromocytoma came while in surgical training under Shipley, who in 1929, surgically removed the first preoperatively diagnosed phaeochromocytoma The patient was a young woman suffering attacks of paroxysmal hypertension There was a resultant complete relief Microscopic examination confirmed the impression that it was a phaeochromocytoma Prior to the time of Shipley's case these tumors had been recognized at autopsy and it had been suggested that they were the cause of the symptoms Surgical exploration had been performed by Mayo who, without a definite preoperative diagnosis, was searching for a splanchnic nerve tumor A phaeochromocytoma was inadvertently discovered and removed with a successful outcome But, it was Shipley's case in which a preoperative diagnosis and definite attack upon a tumor was successfully made for the first time

Even though the phaeochromocytoma is associated with symptoms of paroxysmal hypertension, this need not always be true Snyder and Vick collected 84 cases of phaeochromocytoma appearing in the literature and reported the fourth, fifth and sixth cases of phaeochromocytoma

* Owens, F M Jr Relief of Chronic Hypertension by Excision of Phaeochromocytoma. *Arch Surg* 59 896 1949 This article, published since the beginning of writing of this paper describes in detail a case in the category mentioned above.

(1) *Sympathogonioma* These tumors usually originate in fetal life or in early infancy, being derived from the embryonic sympathogone cells This is usually a highly malignant and fatal type of tumor

(2) *Sympathoblastoma* Here, again, the lesion is usually highly malignant It originates from the sympathoblasts, and occurs chiefly in younger children, and is considered to be a highly malignant sarcoma type of lesion They are called neurocytomas, and neuroblastomas Some of these tumors of the right gland have been shown to metastasize to the liver and have been described under the name of Pepper, while those of the left side tend to metastasize to the skull, and have been referred to as the Hutchinson tumor The work of Anson, *et al*, after a careful study of over 400 cadavers, has shown that the suprarenal arteries are usually multiple However, there is only one vein for each suprarenal gland By a study of these veins and their possible communications they are able to explain how metastasis to various parts of the body may take place Right adrenal medullary neoplasms that metastasize, tend to involve the liver The right adrenal vein empties directly into the vena cava just distal to the hepatic veins Neuroblastomas of the left adrenal medulla frequently metastasize to the skull and thoracic cage The left suprarenal vein empties into the left renal vein which in turn communicates through the azygos to internal mammary and intercostals The left renal vein also communicates with the lumbar and vertebral veins and thence to the skull bones Therefore, there is an anatomical basis for the prevalent type of spread of malignant medullary neoplasms

(3) *Ganglioneuromas* These originate in the mature sympathetic cells, are usually benign, but they become malignant in the form of ganglionic sarcoma

(4) *Chromaffinomas* Unlike the three previous types of tumors of the medulla, the chromaffinomas have a tendency toward alteration of physiology by giving rise to hyper-adrenalism The chromaffinomas may be considered as (a) benign phaeochromocytomas, (b) diffuse hyperplasia of the medulla, (c) malignant phaeochromocytomas, and (d) paragangliomas, outside the medulla

The benign phaeochromocytomas, consisting of mature chromaffin cells, give rise to various types of hypertensive difficulties Bartels and Wall have suggested a classification of the clinical types of phaeochromocytoma on the basis of some typical cases They divide them as follows

Secondly, chromaffinomas may be considered as *diffuse hyperplasia of the adrenal medulla* Sympathicotonia may possibly be considered due to a hypermedullary function with the symptoms of vasomotor instability, tachycardia, exertional hypertension, irritability, excessive perspiration, and exhaustion Crile has performed complete adrenal denervation with reported good results However, these have not been confirmed

According to McGavack, *malignant phaeochromocytomas* are relatively rare lesions and he reports the eighth case of such a tumor He stresses the absence of paroxysmal hypertension in these malignant cases

Paraganglioma is usually used to describe extra adrenal medullary tumors of the chromaffin nature, and hence distinguishes them from the phaeochromocytomas which occur in the medulla proper Smith has recently reported an extra medullary paraganglioma with symptoms of paroxysmal hypertension, and blanching of the finger tips Diagnosis was made and based upon a soft tissue tumor, seen on x ray, which contained calcium and was located at the level of the second and third lumbar vertebrae deflecting the ureter around the mass As is the case of many chromaffin tumors this patient went into shock following the removal of the tumor but by adequate restorative measures she survived

Even though some patients with a phaeochromocytoma have been shown to have a persistent hypertension, the adrenalin hypersecreting activity of these tumors is not a common cause of hypertension or of arteriosclerosis Goldzieher, Green, and others, feel that overactivity of the adrenal medulla may be the cause in some instances Drake, Hibbard and Hellwig conclude from their studies of medullary changes in various diseases that this gland can play a role in the early stages of hypertension

Nor-epinephrine, also known as nor adrenalin or levo-arterenol is a pressor drug that appears to be identical to Sympathin E a regular constituent of the body In normal adrenal medulla, there is present about 80 per cent epinephrine to 20 per cent nor epinephrine However, in hyperfunctioning medullary tumor tissues, there may be a complete reversal of this ratio with an increase of nor-epinephrine by 4 1 over epinephrine

ADRENAL CORTEX

The adrenal cortex, the peripheral portion of the adrenal gland presents so many characteristics that differ from the adjacent adrenal medulla, that their close approximation appears to be a matter of

occurring in children under the age of 13 Two of the children died almost immediately while the third survived the removal of bilateral phaeochromocytomas They stress that there was a continuous, severe hypertension in all three cases rather than the classical paroxysmal episodes

Bilateral phaeochromocytomas occurring in blood relatives have been reported by Calkins and Howard and by Colston with successful outcomes following surgical removal

Bauer and Belt reported a case of paroxysmal hypertension associated with swelling of the thyroid gland, cured by the removal of a phaeochromocytoma and suggest that the intense paroxysmal hyperemia of the thyroid was probably due to sudden rise of blood pressure of the carotid sinus during hypertensive crisis which gave rise to swelling which persisted for some time after the hypertensive attack had quieted down

Phaeochromocytomas are usually well encapsulated, but the capsule is frequently thin and delicate On section, the tumor is reddish-brown in appearance, and microscopically the cells are large and polyhedral, with a coarse granular cytoplasm The characteristic paroxysmal attacks are usually seen to last from five to fifteen minutes associated with some nausea, vomiting, possibly syncope, with a feeling of apprehension and anxiety Death may occur at one of the attacks from heart failure or a cerebral accident The attacks may come on without cause, or result from emotional stress or physical strain In addition to the previously mentioned urographic and perirenal insufflation studies for suprarenal tumors in general, there are available certain tests such as injection of histamine as described by Roth and Kvale in which the drug induces episodes identical with a spontaneous attack A similar hypertensive reaction follows the subcutaneous injection of mecholyl The more recent use of benzodioxan as a test for increased circulating epinephrine and the use of tetraethyl-ammonium bromide or chloride may aid in the discovery of a phaeochromocytoma Once the diagnosis is made, surgical removal of the tumor is indicated to prevent further crisis A transabdominal exposure gives excellent visualization of both suprarenal glands, but it carries a greater mortality rate and higher instance of shock The lumbar approach on the other hand is somewhat easier and less disturbing but allows exploration of only one gland at a time During and following operation, means should be available to combat any immediate crisis or alteration of blood pressure These measures, such as intravenous epinephrine, intravenous infusion of sodium chloride, transfusions of blood, and injection of adrenal cortical extract, may be life-saving

3 Those dealing with the properties of sex hormones (such as estrogens, androgens, and progesterone)

This prelude to the study of the adrenal cortex may excuse some of the present shortcomings of knowledge Many studies of the vast, important and elusive amounts of materials for consideration are still in their infancy

Many factors have influenced the great advancements in the knowledge of cortical activity developed during the modern era which began, according to Gaunt and Eversole, about 1930

(a) The improvement of technique in performing adrenalectomy on experimental animals by Rogoff and Stewart led to better studies than those previously obtained on animals in profound postoperative collapse.

(b) The work of Zwemer in diverting of attention from the concepts that the medulla was the "life sustaining" portion of the adrenal gland and that epinephrine was the sole internal secretion of this organ Kemper recently wrote, "At the turn of the century Oliver and Schaefer added still another change in our concept when they extracted epinephrine and demonstrated its remarkable pharmacologic action 'Certainly,' reflected our medical predecessors, 'this powerful glandular extract is the vital suprarenal hormone and its appropriate use will lead to an effective substitution therapy of the Addison syndrome' This concept lingered for more than a quarter of a century but was finally abandoned with the death of Dr Muirhead of the State of Nebraska, who died of Addison's disease In collaboration with Dr Leonard Rowntree, he submitted himself to an intensive experimental program of epinephrine medication, later recognized as the Muirhead regime He seemed to have proved that no matter how concentrated the dosage, or by what method administered it failed to prevent the downward course of his disease"

(c) The demonstration by Loeb, Harrop and others of the benefits obtained by administration of NaCl to the Addisonian patient It was later shown that these patients could not withstand stress well and that disordered sodium metabolism could not completely explain adrenal insufficiency The latter proved to be a factor which encouraged the investigation of the influence of potassium which had been shown by Hastings and Compere to rise to toxic levels following adrenalectomy Similar to that of sodium, the regulation of potassium metabolism is definitely a major cortical function It has been shown by Harrison and Darrow that the mechanism of sodium loss and potassium retention following adrenalectomy results from a defect in renal tubular function An earlier impression that the characteristic changes in water metabolism as seen in adrenal insufficiency were solely a secondary response to

chance rather than any active inter-dependency between these two structures The adrenal cortex, in close conjunction with the gonads, is derived from the genital ridge and is of mesodermal origin Microscopically, the cortex is seen to consist of three zones The innermost or central zone, is called the zona reticularis, and is in intimate association with the peripheral portion of the medulla The middle zone consists of spongiocytes arranged in parallel columns and is called the zona fasciculata The peripheral zone consists of loops and ball of polyhedral cells and is known as the zona glomerulosa It has been felt that this peripheral zone is the site of growth of the adrenal cortex, and that growth takes place from without in Greep and Deane take exception to this so-called "escalator" theory of cell migration and feel that the cells arise, secrete and die in their respective zones

As has been previously mentioned, the adrenal medulla is supplied by and under the influence of the splanchnic nerves and responds to nerve stimulation or inhibition to a marked degree The cortex on the other hand has no definite response to nerve influence, its action being to a great extent, if not solely, under hormone control

Even though one adrenal gland and the medulla of the opposite gland may be removed life is still possible, but the removal of both adrenal cortices is not compatible with life

PHYSIOLOGY

It is impossible at the present time to make many rigid and dogmatic statements concerning the complete physiology of the adrenal cortex, because much theorizing still exists regarding various functions of this organ. There are, however, a considerable number of impressions concerning cortical activity that have been sufficiently substantiated by intensive investigation so as to allow a discussion to be carried out with a reasonable assurance as to its accuracy. Much of the early information concerning adrenal cortical function resulted from studies made on adrenalectomized animals and Addisonian patients. The symptoms of cortical insufficiency have become well established during the past century Apparently few tissues or organs are unaffected by disfunction of the cortex and many possibilities remain yet to be explored Even though almost every body activity is to some degree affected by the adrenal cortex, most investigators, Gaunt and Eversole, Venning and Brown, feel that certain general functions appear to be outstanding These activities fall into three main groups:

1 Those which affect electrolyte (Na and K) and water metabolism.

2. Those concerned with organic (carbohydrate, protein and possibly fat) metabolism,

which have been isolated, the six listed below are known to possess corticoid properties

1	11-desoxycorticosterone	D O C A.
2	17 hydroxy 11-desoxycorticosterone	
3	Corticosterone	Compound "B"
4	17 hydroxycorticosterone	Compound "F"
5	11-dehydrocorticosterone	Compound "A
6	17 hydroxy 11-dehydrocorticosterone	Compound "E

From the action of these six prepared compounds the over all picture indicates that the 11 desoxycorticosterones prepared as the acetate and known as D O C A deal chiefly with electrolyte metabolism, while the C 11 oxygenated steroids which are called compound A, B, E, and F, deal chiefly with organic metabolism, according to Ingle One must not feel, however, that there is no interdependency because it is felt that there is considerable overlapping of effect between these two functions In addition to the above mentioned compounds there are some which have androgenic, estrogenic and progestational effects, and apparently account for the sex influence At present, the remaining compounds are thought to be inactive (a concept which may soon be disproven)

Because of the nature of adrenal cortical compounds and possible relationship of structure to activity, some knowledge concerning their chemical composition is essential The following explanations may serve to create a better understanding

Chemical substances the names of which have the suffix "-one," are classified as ketones Ketones may be simple or mixed A simple ketone has two identical groupings attached to a carbonyl group, and may be



represented as R C R. Acetone, CH_3-C-CH_3, also referred to as propanone or dimethyl ketone is a good example of the simple type A mixed ketone has two different groupings attached to the carbonyl



group and may be shown as R -C R″ Butanone, occasionally called



ethyl methyl ketone, with C_2H_5 C CH_3 as its structural formula is representative of the mixed variety

Adrenal cortical compounds are steroids These steroids have a definite ring system possessing a basic structure in which the rings and carbon atoms are arranged as follows

the altered electrolyte levels appears to be inadequate Now, according to Selye, Winter, Schweizer, and others, there are indications that compounds produced by the cortex may have diuretic or antidiuretic actions, depending upon various factors Therefore, it appears that changes in water metabolism cannot be explained simply as a passive response to electrolytic changes but may also depend primarily, at least to some extent, on cortical hormone activity

(d) The isolation of cortical extracts, by Swingle, Hartman and others, which would benefit experimental adrenal insufficiency indefinitely Soon thereafter, Rowntree, *et al*, reported the successful revival of a moribund Addisonian patient by the administration of this cortical extract, and the endocrine nature of adrenal cortex activity became established The discovery of cortical extracts stimulated further intensive study of the adrenal cortex function in that the effects of overdosage could be explored, and provided greater means for investigation than the previously utilized "insufficiency phenomenon" which had not been too fruitful

(e) The proposal by Britton, Hartman, Long, Evans, and others, that organic metabolism was under direct influence of the adrenal cortex, stimulated the conception of the multiplicity of function of this gland Prior to these discoveries, the sole function of the cortex was thought to be electrolytic and water metabolism, and that the cortex contained only one hormone It had long been recognized that blood sugar and liver glycogen levels were low in the adrenal insufficiency syndrome but these changes had been considered to be due to the debilitated state of the patient or experimental animal in a moribund condition rather than, as we now know, resulting from decreased activity of the cortex itself

(f) The isolation and preparation of crystallized adrenal steroids marked one of the most outstanding advancements toward solving the problems of the adrenal cortex This work, pioneered by Wintersteiner and Pfiffner, Reichstein, and Kendall, has resulted in the isolation of 28 adrenal steroids to date Therefore, the concepts concerning the physiology of the cortex based on observations made by the induction of adrenal cortical insufficiency and noting the response obtained with the use of extracts of adrenal cortex has been enormously aided by the progress in producing and isolating some of the compounds of this gland With each bit of additional information it becomes increasingly more evident that the adrenal cortex may well be considered to exert some influence over all of the bodily processes, ranging from mild synergism, or antagonism, to complete control Thus far, of the 28 adrenal steroids

which have been isolated, the six listed below are known to possess corticoid properties

1	11-desoxycorticosterone	D.O.C.A.
2	17 hydroxy 11-desoxycorticosterone	
3	Corticosterone	Compound "B
4	17 hydroxycorticosterone	Compound F"
5	11-dehydrocorticosterone	Compound A
6	17 hydroxy 11 dehydrocorticosterone	Compound E"

From the action of these six prepared compounds the over all picture indicates that the 11 desoxycorticosterones prepared as the acetate and known as D.O.C.A. deal chiefly with electrolyte metabolism, while the C 11 oxygenated steroids which are called compound A, B, E, and F, deal chiefly with organic metabolism, according to Ingle. One must not feel, however, that there is no interdependency because it is felt that there is considerable overlapping of effect between these two functions. In addition to the above mentioned compounds there are some which have androgenic, estrogenic, and progestational effects, and apparently account for the sex influence. At present, the remaining compounds are thought to be inactive (a concept which may soon be disproven).

Because of the nature of adrenal cortical compounds and possible relationship of structure to activity, some knowledge concerning their chemical composition is essential. The following explanations may serve to create a better understanding.

Chemical substances, the names of which have the suffix "-one," are classified as ketones. Ketones may be simple or mixed. A simple ketone has two identical groupings attached to a carbonyl group, and may be



represented as R-C R. Acetone, CH_3 C CH_3, also referred to as propanone or dimethyl ketone, is a good example of the simple type. A mixed ketone has two different groupings attached to the carbonyl



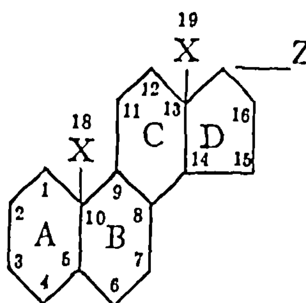
group and may be shown as R'-C R''. Butanone, occasionally called



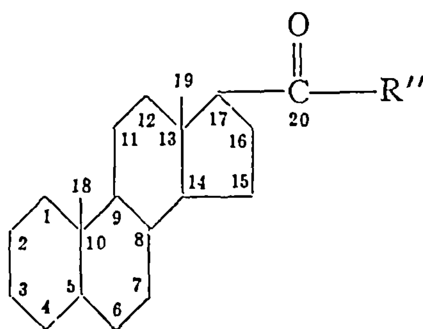
ethyl methyl ketone, with C_2H_5 C CH_3 as its structural formula is representative of the mixed variety.

Adrenal cortical compounds are steroids. These steroids have a definite ring system possessing a basic structure in which the rings and carbon atoms are arranged as follows

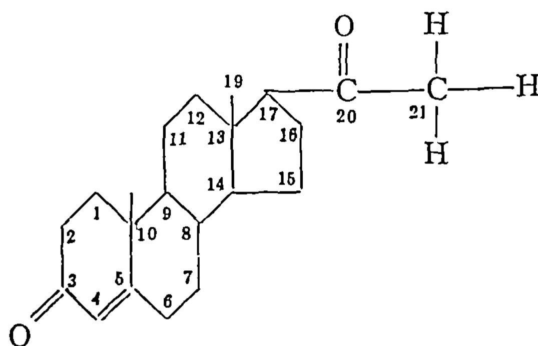
RING SYSTEM OF STEROIDS



X represents a methyl group (CH_3) while Z may possess a wide variation in composition By returning to the consideration of mixed ketones, the steroid ring may be seen to represent R′ of the basic formula, $R'\text{-}\overset{\overset{O}{\|}}{C}\text{-}R''$, i e ,

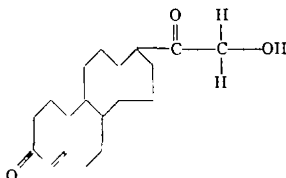


Progesterone, one of the sex hormones, is a steroid that is produced by the ovary and to some extent by the adrenal cortex Considering it as a complex mixed ketone, with slight modification of the basic steroid ring and a methyl (CH_3) grouping at R″, its formula, as represented below may be more clearly understood



PROGESTERONE

All six of the isolated active cortical compounds have CH_2OH instead of CH_3 in the R″ position In the case of 11 desoxycorticosterone (one of the six compounds) the replacement of an H atom by an hydroxyl is the only way it differs in structure from progesterone



11 DESOXYCORTICOSTERONE

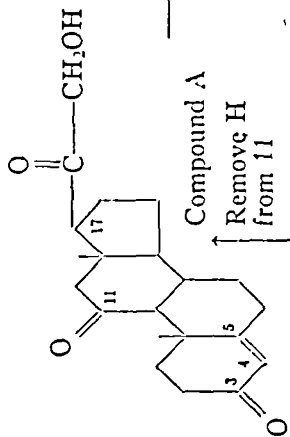
The six cortical compounds thus far isolated which possess activity show very similar structural formulas, the names of which are based on changes in their structure which take place at C 11 and C 17

1 Numbers in their names refer to certain carbon atoms
2 Desoxy means that a hydroxyl group (OH) has been replaced by hydrogen (H)
3 Dehydro indicates oxidation with removal of a hydrogen atom (H) from a hydroxyl group (OH)
4 Hydroxy pertains to the replacement of a hydrogen atom by a hydroxyl group (OH)
5 All six possess the following characteristics
   a A carbonyl ($-\overset{O}{\overset{\|}{C}}$) at C 3
   b Double valence ($-C{=}C$) between C-4 and C 5
   c A C 20 C 21 grouping of $\overset{O}{\overset{\|}{C}}\ CH_2OH$

(g) The recovery of materials in the urine, which are apparently metabolites of various cortical hormones eliminated as waste, or by products, has afforded a method of measuring various activities of the adrenal cortex There are two main types of these urinary corticoids or steroids, namely the 17 ketosteroids, which have a carbonyl group at C 17 and the glycogenic corticoids which biologically resemble the corticosterones

Urinary 17 ketosteroids in the male are derived from both the adrenal cortices and the testes while in the female the cortex is apparently the only source According to *Johnson and Nesbitt*, and Roble

11-dehydrocorticosterone

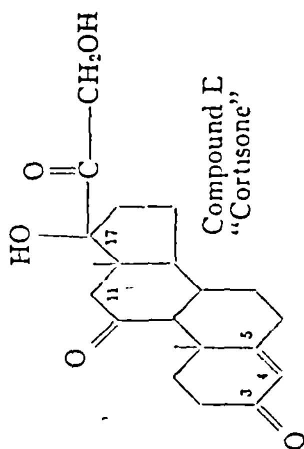


Compound A

Remove H from 11

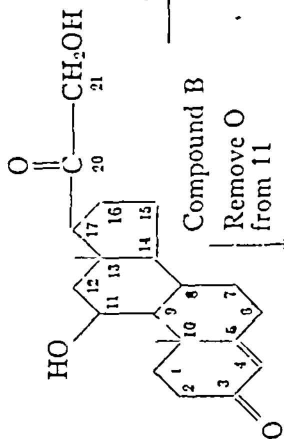
add OH at 17

17-hydroxy-11-dehydrocorticosterone



Compound E
"Cortisone"

Corticosterone

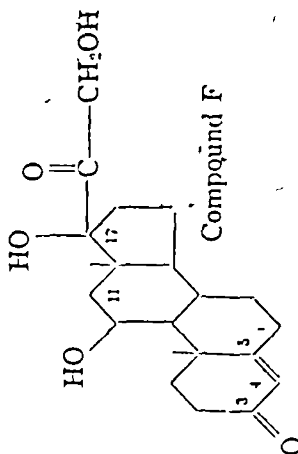


Compound B

Remove O from 11

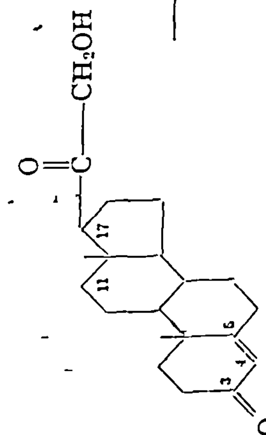
add OH at 17

17 hydroxycorticosterone



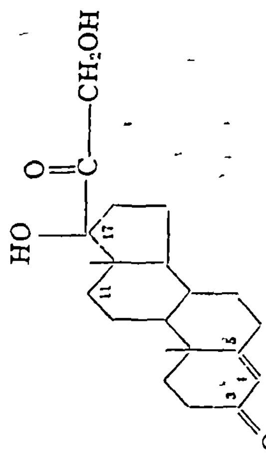
Compound F

11 desoxycorticosterone



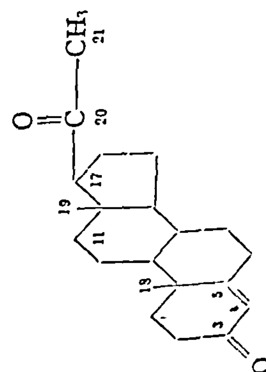
add OH at 17

17 hydroxy-11-desoxycorticosterone



Remove O from 21

Progesterone



and Gibson, values of 17 ketosteroid excretions, measured in milligrams per 24 hours output of urine, are about 5 5 for women and 9 for men, while higher average normal values of 11 and 16, respectively, are reported by Venning and Brown A further breakdown of the 17 ketosteroids is now possible Frame has described a method of fractionalization by which an alpha fraction may be determined The alpha fraction may then be subtracted from the total 17 ketosteroid values and thus, in an indirect manner, the figures for a beta fraction may be obtained It is felt that under normal conditions, the alpha fraction varies between 85 and 95 per cent of the total 17 ketosteroid output, while the beta fraction values are only 5 to 15 per cent According to Venning and Brown, adult levels of 17 ketosteroid excretion in the urine are normally reached at about 18 years of age

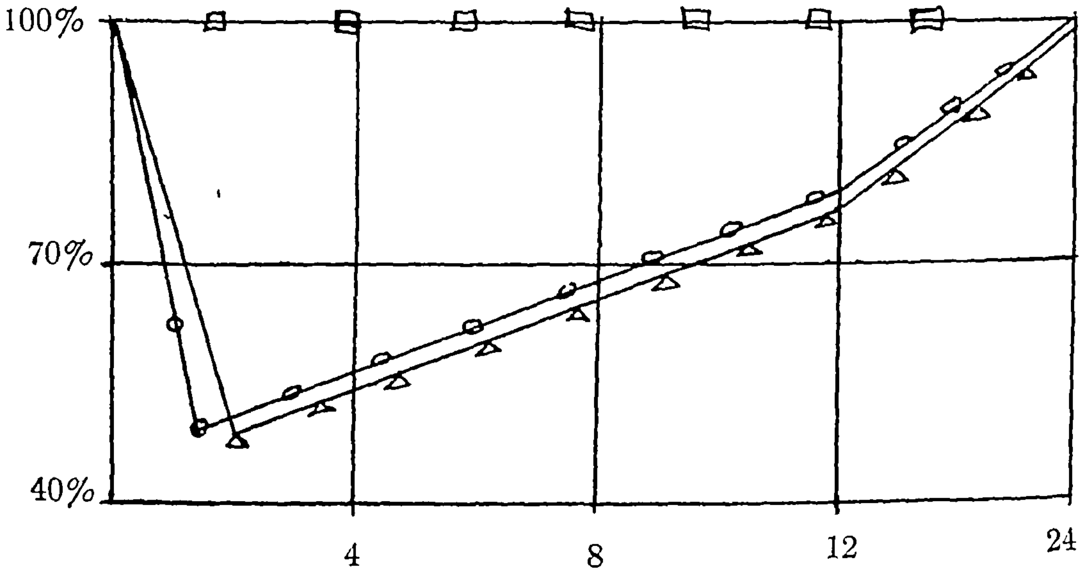
The glycogenic corticoids make up the remainder of the urinary steroids and are capable of prolonging life in the adrenalectomized animal By the assay method of Venning, Kazmin and Bell, based on glycogen deposition in the livers of adrenalectomized mice, these steroids which resemble corticosterone may be measured The authors give normal average values, measured in glycogenic units per 24 hours, as 40 for women and 60 for men It is felt that adult values are reached at a much earlier age for the urinary glycogenic corticoids (about age 5) than for the urinary 17 ketosteroids

The urinary 17 ketosteroids apparently permit evaluation of adrenal androgenic and protein anabolic activity, while the urinary glycogenic corticoids allow assessment of adrenal activity concerned with organic (especially carbohydrate) metabolism. These two types of urinary metabolic by-products result from different types of adrenal functions which are more or less independent of each other

(h) A better understanding of the adrenal cortical response to pituitary control has furthered knowledge in general regarding the activities of the cortex It has been realized for many years that the anterior pituitary gland was concerned with a myriad of body functions, and that almost no cell, organ, nor tissue was not in some way, if only in an indirect manner, under its influence In regard to its influence on the adrenal cortex, particularly in the response of that organ to stress, one must consider it as a part of a tissue, pituitary-adrenal cortex system In general, any stress sustained by the peripheral tissue, initiates a stimulus which acts on the pituitary gland The pituitary in turn secretes adrenocorticotrophic hormone (ACTH) This hormone accelerates the secretory activity of the cortex to produce substances which act to aid the tissue under stress to adapt itself Sayers and Sayers have recently

studied changes in the ascorbic acid and the cholesterol content of the adrenal cortex They had previously demonstrated that the administration of ACTH or noxious stimuli each resulted in gross enlargement of the adrenal cortex Their present work demonstrated that ACTH administration resulted in definite decrease in both ascorbic acid and cholesterol content An almost identical sequence of events resulted from a stress stimulus, such as a non-fatal hemorrhage, provided the hypophysis was intact If, however, the animal was first hypophysectomized, there was no appreciable change in the content of either ascorbic acid or cholesterol The pituitary regulates the concentration of both ascorbic acid and cholesterol in the adrenal gland This may be

TABLE XXVI



Effect of bleeding on adrenal ascorbic acid and cholesterol in the hypophysectomized animal

Effect of bleeding on adrenal ascorbic acid and cholesterol in animals with hypophysis intact.

Effect of ACTH administration on adrenal ascorbic acid and cholesterol in animals with hypophysis intact

Simplified diagrammatic modification from Sayers and Sayers (Sayers, G S and Sayers, M A The Pituitary-Adrenal System, *Ann New York Acad Sc*, *50* 522, 1949)

Ordinate represents percentage content of cholesterol and ascorbic acid in the adrenal gland

Abscissa represents time in hours

graphically represented as shown in Table XXVI, taken from Sayers and Sayers and modified somewhat for simplicity

It is interesting to observe the similarity of response of both ascorbic acid and cholesterol to the stimuli of ACTH and non fatal hemorrhage as shown by Sayers and Sayers Since learning of clinical benefits resulting from ACTH (which is possibly a noxious stimulant and whose prolonged action on the body may later be shown to exert untoward effects) it has made this writer consider the actual value of "blood letting," a procedure considered to be of great worth by the medical world of a century ago It would appear to be quite possible that the clinicians of long ago may have unknowingly created adrenal cortical response by nonfatal bleeding which resulted in increased resistance of the organism and at least temporary improvement of the various maladies

Between the extremes of true hypofunction and hyperfunction of the adrenal cortex, both of which produce fairly well recognized clinical entities, which will be discussed later there exists a vast number of situations resulting from altered function

It is believed that the known active extracts of the adrenal cortex exert qualitatively different effects (Kendall) Impressive information has been obtained by Lewis and Page, Dorfman, and Venning which indicates that there is no difference between the compounds from the adrenal cortex and those produced synthetically

There are certain bodily reactions, such as serologic reaction to antigens, muscle hypertrophy secondary to increased activity prolifera tion of the epidermis resulting from irritation and so on, which are of a specific adaptive nature In addition to these specific adaptive reactions, there are non specific changes, in which the endocrine system plays a prominent part, that occur regardless of the type of damaging agent Selye has given the name general adaptation syndrome" to these non specific protective reactions and divides it into three stages encountered as a result of long continued stress

1 The alarm reaction
2 The stage of resistance
3 The stage of exhaustion

Adrenal cortex changes are pronounced during the general adapta tion syndrome, but may be prevented by hypophysectomy Selye indi cates that numerous clinical entities may belong to the group "diseases of adaptation," and goes on to conclude that if the concept of "diseases of adaptation" proves to be correct, it would establish as factual that endocrine derangements play a crucial role in all major, fatal *syndromes* of internal medicine

It has become quite evident that there is a non-specific physiological response to stresses in general which create in the body some degree of resistance Adrenal cortical hyperfunction appears to be an important phase of this response resulting from stimulation by pituitary adrenocorticotrophin In the absence of the normal pituitary-adrenal action, the response to all stresses is low Even though knowledge of this mechanism is meager, White and Dougherty have demonstrated an influence of adrenal cortical compounds on protein metabolism They have shown that elevated C-11 oxygenated cortical steroid levels resulting from stress, exert influence on the lymphatic system to cause changes in some of its elements with release of gamma globulins into the blood stream for use as protection by the body Long has mentioned that the gamma globulins, which could be identified by an increase in total serum globulin, carried immune antibodies This suggests a manner by which the cortex hormones may aid in resistance to a specific infection It also brings up a question as to whether or not the cortex substances, through the lysis of the lymphatic structures, may liberate products which are in part responsible for resistance to nonspecific stimuli such as cold, trauma and so forth

Braasch found that the non-specific stimuli resulted in increased excretion of urinary non-protein nitrogen and adrenal corticosteroids, but a decrease in 17-ketosteroids

Information concerning the results of a systematic analysis of mental diseases in terms of hormonal dysfunction has been reported recently Pincus has presented strong evidence of altered hormonal activity, even though showing that endocrinopathy does not occur Various tests to determine adrenal cortex response were performed on both normal and psychotic individuals The results of these studies revealed a markedly suppressed or absent adrenal cortical response in the psychotic persons

It has been noted for many years that some arthritic patients seemed to improve if they became jaundiced This was also observed in female patients during pregnancy These observations resulted in a general conclusion that all patients suffering from rheumatoid arthritis possessed some force which lay dormant awaiting proper stimulation Rheumatoid arthritics also appeared to improve following anesthesia and surgical operations Since the adrenal cortex is stimulated by these procedures it was postulated that this stimulation led to the production by the cortex of a hormone that led to improvement of rheumatoid arthritis Hench, Kendall, *et al*, have recently reported the results following administration of 17-hydroxy-11 dehydrocorticosterone ("Cortisone" or "Compound E, Kendall"), and ACTH to 14 patients with

rheumatoid arthritis Improvement of all patients appeared to be dramatic and a state of well being was maintained while they were receiving their medication

Hench, Slocumb, *et al*, administered Compound E to three patients in the acute phase of rheumatic fever This was followed in all instances by rapid disappearance of all symptoms and a return to normal of the sedimentation rate and electrocardiogram They postulated a probable favorable effect on cardiac muscles and fibrous valves in rheumatic fever, which to date has not been helped at all by salicylate medication

It appears that prolonged replacement therapy is essential Because of the difficulty of preparation and the scarcity of supply, it appears that this therapy will have only limited use for the next few years Desoxycholic, a bile acid, has thus far provided the source of the steroids Kendall's recent discovery of newer methods for the synthetic productions of these steroids may be one of the most important events in the history of the adrenal cortex Adrenal cortical replacement therapy may then possibly reach the magnitude and prominence similar to that attained by antibiotic therapy at the present time

Davison, *et al*, have concluded from their studies that there seems to be a tendency toward a considerable increase in 17 ketosteroid excretion in patients with ankylosing spondylarthritis, a disease largely confined to males They feel that in typical polyarticular rheumatoid arthritis a disease more often seen in females, this tendency is not demonstrated

Usually there is a very long interval between the times that work is performed and its results appear in the literature The recording and evaluation of data, the actual writing of the article, the oral presentation at some meeting and the submission for publication may take many months The most current published information must be assumed to be one or two years old. To rely solely on printed articles concerning the adrenal cortex is not in the true sense a source of the most recent information Interest continues to mount steadily concerning this gland The work of Conn, Louis, and Johnston presented at a recent meeting of the American Society for Clinical Investigation is worth noting in regard to glutathione It has been previously shown by Ingle, Li and Evans that the administration of ACTH to animals resulted in glycosuria and hyperglycemia Some of the adrenal steroids were also shown to have a diabetogenic effect Conn and his associates have demonstrated that in the ACTH induced diabetes there is an accompanying decrease in blood glutathione levels They administered large doses of reduced glutathione intravenously and observed a dramatic

decrease in blood sugar and glycosuria Such work as this may have profound effect on the future of medicine

Early, unsubstantiated, and as yet unpublished verbal reports indicate that many of our present conceptions of medicine may be altered considerably In addition to the ACTH and adrenal steroid influence on rheumatoid arthritis and acute rheumatic fever previously referred to, numerous other conditions appear to be related in some way to the adrenals Recent unpublished works indicate beneficial results from adrenal cortical compounds on status asthmaticus, ulcerative colitis, periarteritis nodosa, dermatomyositis, lupus erythematosis, acute glomerular nephritis, anterior poliomyelitis, gout schizophrenia and innumerable other conditions

One would ordinarily hesitate to even refer to unconfirmed verbal information However, under the present circumstances, it seems wise to mention at least that such work is going on and allow the passage of time to bring out either confirmation or contradiction

Knowing that the administration of ACTH results in responses similar to those elicited by various noxious stimuli, it makes this writer wonder whether the overzealous use of this substance may or may not cause serious deleterious effects in the future

HYPOFUNCTION

Deficient activity of the adrenal cortex usually results in relatively clear cut clinical entities These syndromes may be of a chronic or an acute variety depending upon the rapidity of destruction in the adrenal cortex.

CHRONIC ADRENAL CORTICAL INSUFFICIENCY

The chronic form was first described by Thomas Addison almost a century ago and today is commonly referred to as Addison's Disease

Until recently, tuberculosis was considered to be the sole etiological agent Thorn, Dorrance, and Day have now shown that tuberculosis of the cortex causes only about 50 per cent of the disease, while the remainder results from various other conditions (amyloidosis, atrophy, etc) which may destroy the cortex

As destruction of the adrenal cortex progresses, there is concomitant alteration of its physiological processes This altered physiology appears to manifest itself by changes in the following functions

1 *Electrolyte and Water Metabolism* There is a decrease in sodium chloride retention and an increase in water loss

2 *Organic Metabolism* There is diminished carbohydrate preservation, inadequate utilization of fat, and reduced lymphalysis with de-

creased gamma globulin production Long speculates that reduced gamma globulin production results in lowered protein antibody output This may alter the pituitary adrenocortical tissue mechanism to the extent that there is reduced resistance both to specific infections and to stress in general

3 *Androgen Production* In Addison's disease, the reduction of androgenic output is valuable for screening tests Normal values of 17 ketosteroid excretion are quite reliable in ruling out Addisonism

4 *Melanin Deposition* The color of the skin is due to melanin, which is a normal cutaneous pigment It is not clear why increased pigmentation occurs with deposition in the mouth and on the body surface, particularly where there is pressure from belts, garters, etc

As a result of the above changes, certain well defined signs and symptoms may appear In any patient suffering from unexplained weakness, weight loss and gastrointestinal disturbances, chronic adrenal cortical insufficiency should be considered as a strong possibility

A differential diagnosis between Addison's disease and Simmond's pituitary cachexia should not be difficult even though adrenal cortical disturbance is one of the manifestations of the latter condition

In addition to weight loss, marked asthenia, anorexia, nausea, and vomiting diarrhea, and hyperpigmentation, there are additional features and laboratory tests that may aid in establishing a diagnosis There is usually hypotension, and on x ray the heart tends to appear smaller The basal metabolic rate tends to be lowered Serum sodium and chloride are lower than normal, while the serum potassium is elevated The hematocrit is usually elevated, indicating hemoconcentration and dehydration

Other more specific tests include

1 17 ketosteroid determination to evaluate androgenic activity There is a subnormal excretion in Addison's disease

2 Robinson Power Kepler water test in which a strain is created by a "water load" calling forth maximum activity of the gland This test indicates the activities of the adrenal steroids that have no oxygen at C 11

3 Cutler Power Wilder salt deprivation test in which there is reduced NaCl and increased K intake This test also evaluates 11-desoxy corticoid function but is dangerous and may precipitate a crisis

4 Glucose insulin tolerance test in which a strain of insulin induced hypoglycemia is produced This test is to evaluate the activity of the compounds oxygenated at C 11 and concerned with organic metabolism. Hyperpyrexia may develop following the test

5 Circulating eosinophil count and urinary uric acid—Creatinine

Ratio This test also evaluates the hormones that regulate organic metabolism, i e, the steroids oxygenated at C-11 The normal adrenal cortical response to administration of a dose of ACTH results in a decrease of 50 per cent or more in circulating eosinophils and an increase of 50 per cent or more in the urinary uric acid-creatinine ratio The absence of any change indicates adrenal cortical dysfunction

Small doses of epinephrine may be used to perform the same test The epinephrine influences the anterior pituitary to produce increased amounts of ACTH which act in the same manner as if it had been administered The *normal eosinophil count varies from 50 to 250*

6 Therapeutic test This consists of administering desoxycorticosterone acetate (D O C A) for a while, then, unbeknownst to substitute a placebo *The test is evaluated on the clinical response by the patient*

The occurrence of adrenal cortical insufficiency in infants under one year of age has recently been summarized by Chenoweth He was able to collect 10 reported cases In only one of these cases was the destruction of the cortex caused by tuberculosis He emphasizes that some infants that have weight loss, dehydration, vomiting and are not doing well, may have a mild cortical deficiency This appears to be transitory and if treated by replacement therapy for a while they improve and tend to remain well

The treatment of Addison's disease has improved considerably Thorn and his associates state that while in the past, 80 per cent of patients died within two years, it may now be expected that over 50 per cent will survive a period of seven years as have the cases in their series

The following agents have been found useful in the treatment of Addison's disease

1 High salt, low potassium intake
2 Desoxycorticosterone acetate in the form of oral administration, pellet implantation or oil solution injection
3 Adrenal cortical extract
4 Testosterone propionate
5 11-dehydrocorticosterone (Compound A)
6 High caloric diet rich in vitamins

The combination of high salt intake and D O C A therapy should be used guardedly because of the powerful sodium chloride retaining power of the latter Williams feels that by giving testosterone propionate that the action of D O C A is augmented A crisis must be avoided, but in the event it does occur, intensive adequate replacement therapy may be life-saving

ACUTE ADRENAL CORTICAL INSUFFICIENCY

In the event a crisis occurs in an Addisonian patient, it must be assumed that acute insufficiency exists However, this classification is intended to include sudden rapid destruction of the adrenal cortex such as adrenal apoplexy or infarction as seen in the Waterhouse Friedrickson syndrome complicating a hyperpyrexial disease with usually a fatal outcome

HYPERFUNCTION

Neoplasms of the adrenal cortex may in some few instances exert no constitutional effects on the body The great majority, however, especially the adrenal cortical carcinomas, may produce marked changes secondary to disturbances in the endocrine system Unlike adreno-cortical insufficiency which results in a rather classical clinical picture, the hyperfunctioning tumors of the cortex may give rise to a variety of different syndromes Lukens, Kenyon, Kepler, Sprague, Mason Power, and others, have attempted to classify the various conditions that result from cortical over activity As a working basis, one may assume that adrenal cortical hyperfunction results in increased influence by hormones associated with metabolism as well as by some which have a role in sexual control. An excess of either of the above tends to govern the final picture, but there may be many possibilities of different combinations of the metabolic and sexual elements Two other factors of great importance are the sex of the individual and the age at which hormonal changes begin to take place Cahill has presented a classification which seems to be quite adequate He divides adrenal cortical tumors into five groups

(1) Those which cause no recognizable hormonal changes (Such cases have recently been reported by Burgess and Cottler in which the only signs and symptoms present were those of a large mass)

(2) Changes due to excess androgen
- (a) Adult females toward adult masculinity
- (b) Female child toward masculinity
- (c) Male child toward adult masculinity

(3) Changes due to excess estrogens
- (a) Adult male toward femininity

  (This is rare, but McFadzean has reported such a case in detail) One should probably also include those female children with uterine bleeding, enlarged breasts, etc , and other changes toward precocious adult feminization

(4) Changes due to excess androgens and other steroids

Cushing's syndrome associated with sexual changes (mostly in adult females) Flynn has recently recorded seven such cases which he describes as hirsutism of adrenal origin

(5) Changes due to excess of steroids related only to metabolism

Cushing's syndrome without sexual changes (in males and females)

No category is mentioned to include the various hermaphrodites and patients with pseudohermaphroditism In some of these patients, the pathological changes may well be in the adrenal cortex and may have begun to manifest themselves during intra-uterine life Wilhelm, Parson and Segaloff, and others, have described cases of pseudohermaphroditism that had either been undiagnosed or untreated until attaining adulthood, at which time resection of hyperplastic adrenal tissue or removal of a tumor has resulted in an improvement or cure

It is of real importance, according to Walters and Sprague, that patients with a hyperfunctioning tumor of the adrenal cortex and virilism usually excrete a large amount of 17-ketosteroids in the urine whereas if evidence of virilism is minimal or lacking the excretion of 17-ketosteroids may not be elevated This has also been emphasized by Landau, and Crooke and Callow, who discuss the difference in 17-ketosteroids output in "adrenogenital syndrome" and the so-called "Cushing's syndrome" Johnson and Nesbitt, in 1947, were able to collect only 32 cases of adrenal cortical carcinoma in which determinations of 17-ketosteroid excretion had been performed and only a few of these had evaluation of the beta fraction According to Leahy and Butsch, patients with masculinizing changes in which the 17-ketosteroid excretion would suggest that the pathologic change is probably in the adrenal gland A marked elevation of the 3 beta hydroxy-17-ketosteroids per cent (5-15 per cent is normal) to 60 to 80 per cent would tend to indicate that the lesion is probably a tumor rather than hyperplasia

The term "adrenogenital syndrome" was introduced by Gallais in 1912 It is used to designate masculinizing changes without metabolic alterations The patients, usually women, show hypertrophy of the clitoris, hirsutism, increase in musculature, deepening of voice and irregularity or cessation of menses This picture may also result from certain ovarian tumors

In 1932, Dr Harvey Cushing published an original article on basophilic tumors of the pituitary gland He felt that these tumors gave rise to changes that resulted in the following clinical picture

(a) Wasting of muscles and fatigue
(b) Thin extremities

(c) Obese face, trunk and neck (moon face, abdominal apron, and buffalo neck)
(d) Hirsutism
(e) Hypertension
(f) Osteoporosis
(g) Diabetes and polyuria
(h) Ecchymosis
(i) Amenorrhea or impotence
(j) Acne
(k) Purplish skin striations
(l) Polycythemia

The above picture, once thought to result solely from pituitary basophilic adenomas, has been popularly referred to as Cushing's Disease It is felt at present that the pathologic basis may only seldom be a pituitary basophilic adenoma, but that always there is some associated hyperfunction of the adrenal cortex It may seem wise to employ the term "Cushing's Syndrome" which implies a clinical picture rather than the term "Cushing s Disease," which would tend to indicate etiology as well Our present concept has been ably stated by Kepler who, after a thorough evaluation of the subject, concluded, "Is Cushing's disease a primary disorder of the adrenal cortex?—The answer at this time is that I do not know, but it might well be" Albright feels that the adreno-genital syndrome and Cushing's Syndrome are associated with a cancer or an adenoma of one adrenal cortex or with hyperplasia of both adrenal cortices He speculates that the two syndromes represent opposite conditions in that the adreno-genital patient is endowed with an excess of all tissues, while the "Cushingoid" patient is suffering from an atrophy of all tissues

Much remains to be learned concerning the adrenal gland Many of our present conclusions may not stand the test of time, but certainly continued interest and stimulation will be sustained in confirming or disproving the present concepts concerning the physiological and pathological aspects of this extremely important organ

THE PARATHYROID GLANDS

Our knowledge of the very existence of parathyroid glands in the body extends over a relatively short period of time It was during the last quarter of the 19th century that these bodies were discovered Since the time of their detection, much has been learned concerning these little bodies and they have been firmly established as a member of the endocrine system

A brief consideration of the embryologic origin of these glands may

lead to better understanding According to Norris, there are two types of development The bodies that are to appear in the adult as the superior parathyroid gland derive their origin from the fourth entodermal branchial pouch and the fourth ectodermal branchial cleft in conjunction with the lateral thyroid As development occurs, the lateral thyroid and the superior parathyroid glands tend to remain stationary, and in the adult may be seen as a general rule to be adjacent structures

The inferior parathyroid glands have somewhat of a different development in that they arise from the third ectodermal branchial cleft and the third entodermal branchial pouch in conjunction with the thymus glands There then occurs a caudad migration of both the thymus gland and the inferior parathyroid glands down into the neck and upper mediastinum

Weller has suggested that the inferior parathyroid glands be termed the "parathymus glands" on the basis of their origin, migration, and ultimate approximation to the thymus gland itself

In the adult human, the parathyroid glands are usually four in number Each weighs approximately 30 to 50 milligrams They are small, flat, yellowish-brown in color and resemble a kidney in shape They derive their blood supply chiefly from branches of the inferior thyroid artery Histologically, the structure is one of clumps or columns of cells, separated by loose connective tissue According to Norris, six separate and distinct cellular elements may be found However, only three types will be mentioned here first, the large water clear cells, sometimes called "wasserhelle" cells, which are characterized by a large amount of clear protoplasm, second, the chief cells which are rather small, dark staining cells, and third, oxyphil cells which are moderate sized cells with small nuclei, whose protoplasm takes an acid stain

A well established function of the parathyroid gland is the formation and secretion of a substance, parathyroid hormone This hormone is known to exert a controlling effect over the metabolism of calcium and phosphorus in the body

METABOLISM OF CALCIUM AND PHOSPHORUS

During normal activity of the parathyroid gland with proper quantitative secretion of parathyroid hormone into the blood stream, calcium and phosphorus levels remain relatively constant The normal blood level of calcium is about 10 milligrams per cent, and for phosphorus is about 3 milligrams per cent When variations occur in the parathormone output, changes are reflected in the calcium and phosphorus levels of the blood These changes are usually of a reciprocal nature in

which if the serum calcium is elevated the serum phosphorus is reduced, and vice versa There is no known clinical condition in which both the serum calcium and serum phosphorus are elevated However, a low serum phosphorus and low serum calcium may be seen occasionally in rickets According to Keating, great amounts of calcium and phosphorus are stored in the body, and it is a relatively minute quantity of these minerals that is not stored but is circulating in an ionized form in the body which influences vital function The calcium affects permeability of membrane, the excitability of nerve and muscle, the action of the heart, and the coagulability of the blood Phosphorus, in addition to being stored in the bones and teeth, exists in many organic compounds, and is actively involved in numerous metabolic processes Even in the blood only about half of the calcium and phosphorus is in an ionized state, but is in concentration close to the precipitating point Calcium and phosphorus are precipitated when acted upon by enzymes such as alkaline phosphatase An early concept of the action of parathyroid hormone was associated with calcium by a primary action on the skeleton However it is now felt that the parathyroids have their effect on phosphorus rather than calcium by its action on the kidneys The action is primarily on tubular reabsorption of phosphorus, but there is still some evidence that a secondary direct effect may occur in the bones Albright has emphasized that a decrease in the output of parathyroid hormone would result in diminished excretion of phosphorus in the urine, increased serum phosphorus, decreased serum calcium, and decreased urinary excretion of calcium He feels that parathyroid hormone increases urinary excretion of phosphorus followed by diminished serum phosphorus level The lowered serum phosphate level would permit more calcium to enter the serum because of decreased saturation The additional calcium would elevate the level for this ion, and in turn this would lead to increased calcium secretion in the urine In other words the parathyroid hormone does not affect the skeleton directly but has a primary action on the kidneys

Even though it may appear that the parathyroid hormone has a direct action on the kidney, there is evidence that some action may take place on the bone primarily When parathyroid hormone has been injected into the experimental animal following nephrectomy characteristic bone changes and serum calcium elevation do take place (Ingalls *et al*)

According to Baker and Leek, unlike many of the other endocrine organs the parathyroid gland is not under the control of the hypophysis They found that large doses of estrogen to young rats caused hyper

ossification A similar histological modification could be induced by administration of parathyroid hormone In the hypophysectomized rats the hyper-ossification did not occur They then injected estrogen into normal and parathyroidectomized rats which resulted in hyper-ossification in all instances Since hypophysectomy prevented this hyper-ossification, it was assumed that the hypophysis was essential for the phenomena, but that the presence of the parathyroids was unnecessary and concluded that the secretion of a parathyrotrophic factor by the hypophysis need not be postulated

Certain clinical changes occur in response to an inadequate or to an excessive secretion of parathyroid hormones by the parathyroid glands

HYPOPARATHYROIDISM

Hypoparathyroidism, or diminished secretion of the parathyroid hormone, may be spontaneous as described by Drake, *et al*, Keating, and others, or result from surgical extirpation of the parathyroid glands themselves There is a third possibility known as "pseudo-hypoparathyroidism," which clinically is identical but differs from true hypoparathyroidism in that there is no response when given parathormone, biopsies exhibit normal parathyroid glands, and all respond to dihydrotachysterol (Albright) Hypoparathyroidism is reflected by a decrease in the serum calcium, an elevation of the serum inorganic phosphorus and a decrease in the urinary calcium output The clinical manifestations are those known as tetany, which is a condition in which local or general spasm of skeletal muscles occurs either spontaneously (manifest tetany) or only on the application of external stimuli (latent tetany) Latent tetany may be exhibited by Chvostek's sign which consists of spasm of the facial muscles on tapping over the facial nerve, or by Trousseau's sign, which is muscular spasm of the hand resulting from pressure over the forearm Clinically, tetany may result not only from hypoparathyroidism, but also from alkalemia which may result from excessive pulmonary ventilation, with washing out of too much volatile acid, such as carbon dioxide, profuse vomiting from any cause with abnormal loss of a fixed acid such as hydrochloric acid, or by excessive intake of alkali

In practically every form of tetany, one or both of the following chemical alterations of the blood exist one, lowering of the total calcium content, or the amount of calcium in the ionic state, two, some alteration in the concentration of other ions, especially decreased hydrogen ion concentration, or increased phosphate and bicarbonate In

general alkalemia tends to diminish the ionized fraction of serum calcium and favors tetany The clinical manifestations of hypoparathyroidism are essentially numbness and tingling of the fingers toes and mouth There may be the sensations of warmth extending over the body Anxiety and apprehension enter the picture Carpopedal spasm resulting from contracture of the muscles of the hands and feet is quite characteristic of tetany Laryngospasm may occur, causing dyspnea Generalized convulsions coma and death may result It is felt that the decreased calcium ion results in irritability of the peripheral motor nerves causing spasm that it affects the brain stem, resulting in convulsions and that it stimulates the vagus nerve giving rise to spasms of the esophagus and cardia

Physiologic principles govern the treatment of hypoparathyroidism These principles are based on adequate supply and utilization of calcium The supply of calcium may be either in the form of a diet high in calcium and low in phosphorus intravenous injection of calcium, or calcium medication by mouth Better utilization of calcium may be obtained by the use of parathormone which is a protein parathyroid hormone However, this substance cannot be taken by mouth, and frequently patients build up such a tolerance as to become parathormone fast Large doses of Vitamin D may be utilized on the basis of increasing calcium absorption from the gastrointestinal tract However, this substance has little effect on the urinary excretion of phosphorus Dihydrotachysterol, a lipid sterol, which is readily absorbed from the gastrointestinal tract and can be taken by mouth only slightly increases calcium absorption from the intestinal tract however, it has a marked effect in stimulating increased urinary phosphorus excretion This drug also known as A T 10 has the advantage by increasing urinary excretion of phosphorus thereby lowering the serum phosphorus content, allows the increased calcium content to be taken up by the blood As yet little success has been obtained following homogenous parathyroid graft and there is little evidence to support the recently suggested subcutaneous implantation of heterogenous tissue

HYPERPARATHYROIDISM

Hyperparathyroidism is considered to be either primary or secondary It is the primary variety in which we have pathological changes in the parathyroid gland resulting in chemical changes and giving rise to the clinical picture of hyperparathyroidism The secondary variety of hyperparathyroidism occurs as a secondary reaction to disease of some

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other organ, particularly the kidney This hyperplasia is different, histologically, chemically, and clinically, and may be considered a response reaction rather than a causative phenomenon

It is the primary hyperparathyroidism with which we are so concerned The chemical findings in the blood and urine are exactly the reverse of those found in hypoparathyroidism With excess secretion of parathormone, the serum calcium becomes elevated, the serum phosphorus is decreased, and increased calcium secretion in the urine occurs When there is too much parathormone present, the kidneys are stimulated to excrete phosphorus with the resulting increased phosphorus content in the urine Pathologically, there are two separate and distinct types of lesions which give rise to the clinical picture of primary hyperparathyroidism First, there is hyperparathyroidism resulting from an adenoma of one or possibly more parathyroid glands Histologically, the lesion is a tumor involving in most instances the chief cell and on rare occasions the oxyphil cells The other lesion giving rise to primary hyperparathyroidism is a diffuse hyperplasia of the *Wasserhelle* or water clear cells and in which all of the parathyroid glands are diffusely and more or less equally involved In 1947, Norris was able to collect and review 322 cases of adenoma of the parathyroid appearing in the literature At the same time, according to Black and Sprague, Keating had found 24 well documented cases of hyperparathyroidism resulting from hyperplasia of the water clear cells From these figures reported at about the same time it would indicate that an adenoma of the parathyroid giving rise to clinical manifestations occurs about 13 times as frequently as the so-called diffuse hyperplasia It must be stressed at this point that if the primary pathology is a hyperplasia or an adenoma with resultant hyperparathyroidism, there is no difference in the clinical manifestations of these two processes As will be pointed out later, the surgical management of hyperparathyroidism differs markedly, depending upon the primary lesion The clinical manifestations of hyperparathyroidism of a primary variety are chiefly those involving changes in the bone, changes in the kidney, changes in the muscular system, and metastatic calcification Bone changes are the results of demineralization by the loss of calcium and phosphorus excreted in the urine Following demineralization, rarefaction takes place with the formation of cysts which become filled with fibroblasts, resulting in osteitis fibrosa cystica, and it is now felt that even though it may be a manifestation of hyperparathyroidism it is not necessarily synonymous with it Teeth changes may occur on the same basis as mentioned

Because of the increased excretion of calcium and phosphorus in the

urine in marked concentration, precipitation occurs occasionally with the formation of renal stones Depending upon the site of the stone, various renal symptoms may predominate the picture In the presence of recurrent renal calculi, one should suspect hyperparathyroidism

Because of the excess of ionized calcium in the blood stream, neuromuscular symptoms such as fatigue loss of muscle tone, weakness, lassitude, and generalized muscular flaccidity may result

Mulligan in a discussion of metastatic calcification described a condition in which calcium salts are deposited in tissues previously normal, but with a tendency toward alkalinity such as the lungs, kidneys, gastric mucosa, etc It is in these tissues where the excretion of acids results in a more alkaline tissue reaction which results in the precipitation of calcium salts In his discussion of five types of metastatic calcification, he refers to the condition associated with primary neoplasm of the parathyroid as one of the group The other four listed included metastatic calcification (1) bone disease, (2) chronic renal disease (3) hypervitaminosis D, and (4) those due to uncertain etiological factors

Waife has recently suggested hyperparathyroidism as a cause for partial heart block.

The Sulkowitch test is based on the formation of an insoluble salt by the reaction of calcium and oxalic acid In patients with elevated urinary excretion of calcium, the Sulkowitch reagent containing oxalic acid is added to the urine When 10 cubic centimeters of urine are mixed with 5 cubic centimeters of the reagent, a blood calcium level of 8 milligrams per cent or above will result in varying degrees of turbidity, indicating a positive reaction and an increased serum calcium This test is also valuable for the ease by which it can be run for patients suffering from hypoparathyroidism and who are receiving high calcium diets vitamin D, and A T 10 The patients can run the test upon themselves and maintain their calcium output at a moderate level, thus avoiding the difficulties of excess A.T 10 administration

Hyperparathyroidism is truly a surgical disease Mandl in 1925 made the first successful attack on hyperparathyroidism by removing a tumor of the parathyroid gland It has been since that time that Norris has been able to collect 322 cases of parathyroid adenoma It was in 1938 that Albright, Sulkowitch, and Bloomberg reported for the first time six cases of hyperparathyroidism, due to hyperplasia of the parathyroid tissue From this we may see that the surgical management of hyperparathyroidism is in its infancy

The anticipated goal to be achieved in surgical attack of hyperpara

thyroidism is either to remove the entire adenoma, or occasionally adenomas, or to remove sufficient amount of hyperplastic tissue to abate the symptoms of hyperparathyroidism without causing a state of hypoparathyroidism to exist Since the clinical manifestations of both adenoma and hyperplasia are identical, differentiation is only made at the operating table, and it is strongly suggested that a frozen section be performed to guide the ultimate management By frozen section examination, the differentiation between adenoma and hyperplasia is made, and the ultimate surgical course is thus directed

The discovery and removal of a parathyroid adenoma may be expected to give complete relief of symptoms If on frozen section no hyperplasia exists and a tumor is not found, the surgeon should make an extremely careful search for such a tumor, otherwise repeated exploration of the neck may become necessary A helpful point has been emphasized by Cope, Lahey, Azpuru, and Black, and others, which consists of using a vascular pedicle from one of the inferior thyroid arteries as a possible guide to a low lying or ectopically placed parathyroid gland that has developed into an adenoma Following the removal of a parathyroid adenoma, one should be prepared to combat symptoms of hypoparathyroidism Due to the fact that the adenoma has assumed the function of over-activity of parathyroid gland, the remaining normal gland has secondarily become somewhat inactive It is for this reason that 24 to 36 hours following the removal of an adenoma, a state of hypoparathyroidism may ensue and exist until such time that the normal parathyroid tissue assumes adequate activity

If at operation a state of hyperplasia of all the parathyroid tissue is discovered by frozen section examination, then the surgical attack is one of removing all but a certain amount of parathyroid hyperplastic tissue It has been felt that approximately 250 milligrams of tissue should be left behind, because when 500 milligrams or more remain, symptoms of hyperparathyroidism may persist Apparently, hyperplastic tissue tends to stay somewhat stationary In other words, the remaining hyperplastic tissue left behind does not tend to regress back to normal with loss of its hyperplastic quality and give rise to hypoparathyroidism On the other hand, the tendency for hyperplastic tissue to regenerate and produce recurrent hyperparathyroidism may be considered unlikely in view of prolonged cures which have resulted following incomplete removal of the hyperplastic tissue

In general, the adenomatous tissues of the parathyroid gland giving rise to hyperparathyroidism are on the whole benign The occurrence

of a malignant lesion associated with symptoms is somewhat un Also, the recurrence of parathyroid adenomas following removal is unusual, but occasional cases are reported by Burk and others

Since the outlook of hyperparathyroid patients has been so brightened by the surgical attack, an earlier diagnosis of the condition should be strived for, but can only be accomplished by the increased awareness of the physician and the more frequent utilization of the Sulkowitch test

THYMUS GLAND

Even though extensive investigations continue to be carried out, present knowledge concerning the thymus gland is meager The gland originates from the ventral diverticulum of the third and sometimes the fourth branchial clefts and descends in the neck to the superior medias tinum It is epithelial in origin, but soon assumes a lymphoid char acter Whether or not the thymus gland is truly an organ of internal secretion is still debatable However, until more proof to the contrary becomes available, and since variations do occur in the thymus when other ductless glands undergo changes, it is difficult to deny this organ a position in the endocrine system

A phrase quoted by Clagett and Root so well presents the problem of the thymus that it bears repeating "The thymus gland has remained an enigma Endocrinologists have wooed it in vain Physiologists and pathologists have drawn away from it baffled Not even the anatomist or histologist have spoken of it with their customary precision For we are still uncertain whether it has any real existence in the normal adult, and whether the main cells of its medulla are to be regarded as epi thelial or endothelial"

The coexistence of thymic abnormalities associated with myasthenia gravis appear too frequently to be judged coincidental This has led to the belief that myasthenia gravis is due to alterations in the thymic gland

MYASTHENIA GRAVIS

There is strong evidence that the nervous system transmission of im pulses from one neurone to the next depends upon the formation of ace tylcholine at the synapse This chemical transmits the impulses to the next neurone and on to the end of the chain There is present at the synapse cholinesterase which immediately destroys the acetylcholine and allows the synapse or motor end plate to rest until the next stimulus arrives This process occurs throughout the entire central and peripheral

nervous system except in the post-ganglionic sympathetic nerves which have their own chemical sympathin It is considered by Schwab and Chapman, Richter, Keynes, and others, that myasthenia gravis is a metabolic disease in which the transmission of the motor nerve impulses at the myoneural junction is blocked by interference with the action of the transmitter acetylcholine upon the muscle fibers Normally the cholinesterase destroys excess acetylcholine and thus balances the action of voluntary muscle, allowing a rest period between impulses In myasthenia gravis, the production or action of acetylcholine is inhibited in such a way that many impulses are blocked

In 1934, Dr Mary Walker, realizing that physostigmine would tend to neutralize the effect of curare, and that the symptoms of myasthenia gravis were similar to curare poisoning, then deduced that physostigmine would be of benefit in myasthenia gravis Her original paper described the effects of physostigmine on three patients suffering from myasthenia gravis This has been a monumental contribution to the medical history of this disease Neostigmine (U S P), also called prostigmine (Roche), was first synthesized in Switzerland in an effort to obtain a drug less toxic than physostigmine (Eserine) but having similar action Neostigmine and physostigmine act in the same way Both of them depend upon the presence of acetylcholine at the myoneural junction These drugs act by inhibiting the cholinesterase which in itself acts as an inhibitor to the action of acetylcholine Thus, by depressing the cholinesterase there is strengthening of the action of the acetylcholine in the effector organ In myasthenia gravis, there is considerable evidence that the mechanism is an imbalance in the chemical processes of the motor end plate If there is no disturbance of end plate physiology neostigmine has no beneficial effect on striate muscle whether it be healthy or diseased It is the "nicotinic effect" on voluntary muscle that is the basis of effectiveness of neostigmine in myasthenia gravis Neostigmine, however, has a "muscarine effect" in which it stimulates smooth muscle causing constriction of the pupil, increased mobility of the stomach and intestinal tract, and contraction of the bladder It also dilates most of the blood vessels, affecting arterial rather than capillary It is for this reason that atropine, a parasympathetic inhibitor, is used to avoid the side effects From results obtained through animal experimentation, Torda and Wolff, and Trethwie and Wright, suggest that the thymus may influence the synthesis of acetylcholine and probably explain the clinical manifestation of patients with myasthenia gravis Stoerk and Morpeth, and Welsh and Hyde have been unable to confirm these conclusions McEachern feels that the thymus produces a curare-

like substance which interferes with the action of acetylcholine

At the present time we are still in the experimental stage with slight but quite definite indications that there is some relationship between the thymus and myasthenia gravis

Viets, based on a study of over 125 patients with myasthenia gravis, states that about 25 per cent of patients will do remarkably well on moderate amounts of neostigmine medications or may have prolonged and even complete remission In his study 30 per cent of the patients were over 50 years of age at the time of their initial symptoms He stresses that by using diagnostic ampules consisting of neostigmine methylsulfate with atropine sulfate they have established that the drug is a specific antidote for the curare like symptomatology of myasthenia gravis Amyotrophic lateral sclerosis, bulbar palsy, and some of the muscular dystrophies may respond to neostigmine but to a much less degree He also emphasizes that dysphagia may often be the presenting symptom and one of the most common symptoms of myasthenia gravis When dysphagia is a symptom of myasthenia gravis, the response to neostigmine is observed under the fluoroscope and the patient is seen in the act of swallowing thus providing a diagnostic test In no other disease will swallowing be improved as a result of the test, as response in patients without myasthenia gravis is negligible

The use of Di Isopropyl Fluorophosphate (D F.P) in the management of patients with myasthenia gravis has not been an entirely satisfactory project according to Comroe, *et al* and Wilson Di Isopropyl Fluorophosphate or D F P , as it is commonly known, is a compound completely unrelated chemically to neostigmine or physostigmine, but has been shown to produce marked intermission of serum, red cells, muscle, and brain cholinesterase for a long period of time Because of the pronounced and prolonged anti-cholinesterase action, it seemed worth evaluating on patients with myasthenia gravis Even though it was possible with D F P to lower the plasma cholinesterase to zero, it produced less improvement than did neostigmine Wilson feels that the changes in the blood do not reflect the state of affairs at the myoneural junction The failure of the expected response of D F P , an anti cholinesterase agent, in the treatment of myasthenia gravis makes one question whether or not inadequate synthesis of acetylcholine or the presence of an antagonistic curare-like substance is the entire cause of myasthenia gravis Most of the authors find that D F.P is somewhat toxic thus precluding large doses

Knowing that amino acids and proteins had been found to increase acetylcholine synthesis in vitro, Torda and Wolff, accepting the concept

that much of the symptomatology in patients with myasthenia gravis could be explained by decreased acetylcholine synthesis, investigated the effects of infusions of amino acids on patients with myasthenia gravis They were able to show that the known decline of the amplitude of muscle action potential following prolonged indirect stimulation was prevented by infusions of amino acids However, they could find no therapeutic implication justifiable to the preliminary experiment There are other drugs that have been used in the management of patients with myasthenia gravis However, the benefit they would exert is nullified by side reactions of a toxic nature Ephedrine sulfate has a tendency to cause wakefulness Potassium chloride has such a bad taste that its continued use becomes obnoxious Guanidine hydrochloride may result in parasthesia

Myasthenia gravis patients are made much worse by curare and quinine, and these drugs particularly should be avoided even as diagnostic measures

THYMECTOMY AND MYASTHENIA GRAVIS

Blalock, in May, 1936, performed the first successful removal of a tumor of the thymic region in an attempt to influence the course of myasthenia gravis At that time, only four previous attempts had been recorded, all of which were unsuccessful In 1941, Blalock, Harvey, Ford and Lilienthal reported the first effort to combat myasthenia gravis surgically in the absence of a thymic tumor Of their six cases, there were no tumors Hyperplasia existed in one Three operations resulted in improvements, two were of no benefit, and one patient died

Based on a study of 100 glands, Murray and McDonald believe that the incidence of myasthenia gravis among patients with a thymoma is nearly 100 per cent Adams and Allen report the removal of a thymoma in a young man who had not developed symptoms of myasthenia gravis They also refer to another case which had an upper mediastinal tumor which later was proven to be a thymic tumor, but who did not develop symptoms for over a year after the presence of a tumor was documented These authors feel that the incidence of thymic abnormalities found at autopsy of patients dying of myasthenia gravis is about 50 per cent, and may be somewhat higher if sought for with greater care

Keynes has recently reported 100 thymectomies for myasthenia gravis In only 12 of his cases was a thymic tumor demonstrated Of these 12, the results were not good Of the remaining 78 patients without tumor, the results were much better Of 63 cases followed long enough for adequate assessment, 44 are quite well, 16 are normal when

taking only small amounts of prostigmine 18 are slightly improved, and there are only five who showed no improvement In other words best results were obtained in those patients suffering from myasthenia gravis who had not developed a tumor and were in the younger age group with relatively short histories At this writing Blalock feels that his results are somewhat comparable to those of Keynes but in general does not feel too enthusiastic about thymectomy for the management of myasthenia gravis except in very selected cases

Clagett and Root suggest three types of approach for the surgical management of the thymus first a transcostal anterior approach through the third and fourth ribs just to the right of the sternum, second the posterolateral approach with resection of the fifth rib on the right side from the right of the midline around quite far anteriorly, and third, sternum splitting approach It appears that the sternum splitting approach has definite advantages These authors stressed the necessity to maintain prostigmine and other drugs to combat myasthenia gravis symptoms postoperatively

Long and Allen suggest that the surgical removal of benign thymic tumors might well prevent the occurrence of malignancy at a later date but it is certainly not possible to predict which of these tumors may or may not become malignant They also suggest the early removal in symptom free patients as a means of averting the subsequent onset of myasthenia gravis

According to Adams and Allen, with rare exceptions, tumors of the thymus associated with myasthenia gravis have been benign Myasthenia gravis is extremely unusual in association with malignant thymus tumors

Long and Allen suggest the possibility that in many instances apparent enlargement of the thymus in children may be due to faulty position of the child while taking the x rays It has been shown that apparently enlarged thymus glands can be made to disappear simply by straightening or extending the child s neck and dorsal spine while taking the x ray Good s study of 100 patients with myasthenia gravis was able to show 17 mediastinal tumors, 14 of which were confirmed by operation or autopsy

Hardiman and Bradshaw revealed that a summary of the literature on the value of surgery in cases of myasthenia gravis has given approximately 50 per cent of these patients some improvement. Campbell suggests that possible lack of improvement in myasthenia gravis following thymectomy may persist because of the muscles that have undergone pronounced atrophy and fibrosis and could not be regenerated because

of their state of degeneration This would occur in those who had a long standing course of disease prior to operation

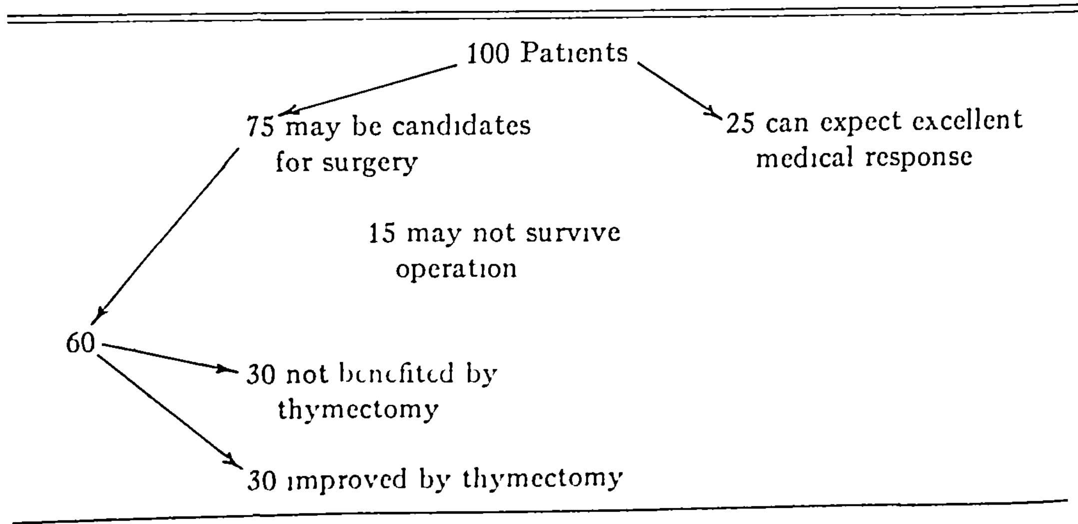
It has been stated that tumors of the thymus gland associated with myasthenia gravis have been with rare exceptions benign lesions It is extremely unusual to find myasthenia gravis associated with a malignant tumor At present, it is considered that malignant tumors of the thymus gland are in general inoperable They characteristically invade the adjacent great vessels and other vital structures, thus rendering their complete extirpation incompatible with life We have only x-ray therapy as a palliative means for their temporary control

It may be well to recapitulate some figures for better understanding The incidence of myasthenia gravis symptoms associated with thymic tumors is said to be nearly 100 per cent The incidence of thymic tumors in patients suffering from myasthenia gravis is thought to be about 50 per cent, and it is felt that if a more careful search were made, the percentage would be higher It has been stated that about 25 per cent of all patients with myasthenia gravis can be expected to do remarkably well on moderate doses of neostigmine medication, or may have prolonged and even complete remission It is thought that an over-all mortality in thymectomy is approximately 25 per cent For those people surviving operation, about 50 per cent can expect some degree of improvement

From the above figures, using 100 hypothetical cases of myasthenia gravis, the following picture may be obtained as will be shown in the graphic chart shown below Twenty-five of these patients could be

Table XXVII

Expectancy in 100 Myasthenia Gravis Patients



expected to have complete control on neostigmine or have complete remission The remaining 75 may possibly be considered candidates for thymectomy Fifteen of the 75 may not survive the operation Of the remaining 60 patients who survive 30 may receive no benefit whatsoever, and the remaining 30 receive some improvement In other words, of every 100 patients with myasthenia gravis, only 30 patients can be expected to be benefited by thymectomy

There is no evidence to indicate that x ray therapy over the thymus gland has any benefit in the symptomatology of myasthenia gravis

Prostigmine in myasthenia gravis appears to be somewhat inadequate when its efficacy is compared with the use of insulin in patients suffering from diabetes On the other hand, thymectomy is also discouraging when the results are compared with surgical correction of patients with hyperthyroidism and hyperparathyroidism The answer is still somewhat obscure and the problem should stimulate the continued research and investigation in hopes of obtaining a better solution

STATUS THYMICOLYMPHATICUS

Long and Allen, Russell, and others feel that the discussion of status thymicolymphaticus is a closed issue and they feel that there is no good evidence that such an entity exists On the other hand, Carr has recently reported 520 cases of such deaths in children below the age of 10 years In this excellent and comprehensive review 49 cases were found in which the patient died of a condition arising from or directly associated with pathological changes in the thymus gland and lymphatic system He has suggested a new and descriptive term, which is "thymico asthmaticus," and feels that this name is a more applicable one He states that enlargement of the thymus gland, lymphatism, hypoadrenalism, and similar related conditions have been displaced even from secondary positions of importance as causing disease and death These have been thrown into disrepute by articles in the medical literature which are apparently based more on precedent and fashion than on observation The popular attitude that there is no such thing as 'thymicolymphaticus' can quickly be dissipated by autopsies of children A widespread belief that an enlarged thymus in itself would not cause asphxyia by tracheal and auricular compression and distortion can be disproved at necropsy whenever studies are done on cases of sudden death in children It may be well to view status thymicolymphaticus with an open mind at least for the time being Undoubtedly, the term has been used loosely and it may be that such diagnostic abuses have in the main been responsible for the disrepute of the thymus

MACROGENITOSOMIA

Weber and Wohl have recently described a 14½ year old boy who had marked precocial sexual development associated with a superior mediastinal tumor They suggest this as a new syndrome and call it "macrogenitosomia" of the "juvenile Hercules type" with tumor in the superior mediastinum Even though on x-ray there is a demonstrable tumor in the mediastinum, there is no proof that this tumor is of thymic origin, and there is no evidence to completely rule out some other causative agent of one of the other endocrine organs as being the etiology for the unusual sexual development

THE PITUITARY GLAND

The pituitary gland (hypophysis) is encased in the sella turcica of the sphenoid bone located just behind and below the optic chiasma The gland is composed of an anterior and a posterior lobe Each lobe is of ectodermal origin but derived from a different site The anterior lobe arises as a hollow outpouch of the primitive buccal cavity known as the craniopharyngeal duct or pouch of Rathke, while the posterior lobe originates from the floor of the third ventricle The lobes of the pituitary gland differ so greatly that their separate consideration seems mandatory

ANTERIOR PITUITARY

It is felt that the pituitary gland is the master organ of the endocrine system, and that this control is due for the most part to the activity of its anterior lobe The physiological effects attributed to the anterior pituitary are believed to result from its affect on some of the other endocrine organs as well as by its direct action on peripheral tissues Whether the antuitary is the control tower of the endocrine system does not seem to be really an important issue providing one fully realizes the influence of other glands of internal secretion not only on the pituitary itself, but on the remainder of the endocrine system In Addison's chronic adrenal cortical insufficiency, co-existing atrophic changes have been noted in the chromophilic elements of the anterior pituitary On the other hand, primary anterior pituitary deficiency diseases appear to cause some atrophy of the adrenal cortex

The anterior lobe is made of three types of cells The names, chromophobe, acidophil and basophil are used to describe the various types and indicate the staining characteristics of the cell granules Possibly the chromophobe cells, which make up about 50 per cent of the antuitary and appear to have no known function, may represent an early stage in the development of the other two types

Recognizing the interdependency of activity of the endocrine system, the mention of certain pituitary functions infers that the organ plays an important role but is not necessarily the sole agent Hypophysectomy for the most part results in changes attributed to the withdrawal of anterior lobe secretions Arrested growth, atrophy of the gonads, suppression of milk secretion, atrophic changes in the other endocrine glands and decreased resistance to infection make up the expected changes following removal of the hypophysis

There is strong evidence that at least six different internal secretions are produced by the anterior pituitary

These hormones are listed as follows

1 Somatotrophic
2 Gonadotrophic (which acts on germ cell derivatives)
3 Gonadotrophic (which acts on connective tissue cell derivatives)
4 Lactogenic.
5 Thyrotrophic.
6 Adrenocorticotrophic

It is questionable whether the pineal, thymus or parathyroid glands are influenced to any extent by the pituitary There may be hormones from the anterior pituitary that influence the various processes of metabolism in general, but it seems more likely that the metabolic processes are under joint control of all the endocrine organs

SOMATOTROPHIC HORMONE

Pituitectomized young animals do not grow to normal size even under the best nutritive regime On administration of the antuitary extract to such stunted animals growth is restored The growth hormone is thought to be derived from the eosinophil cells, for adenomas found in cases of gigantism and acromegaly are most often composed of these cells The mechanism by which the growth hormone produces its effect is unknown

Deficiency of the anterior pituitary growth hormone occurring in the young results in dwarfism An excess of growth hormones in early life results in gigantism, whereas in the adult it causes acromegaly Both of the latter conditions can be produced experimentally in animals by injecting antuitary extract. There is a maximum response beyond which no increased affect can be obtained with increase of dosage

Clinical use of growth hormone alone is seldom indicated because subnormality of the pituitary usually involves more than one of its hormones In pituitectomized animals there is a better response when other hormones such as the thyrotrophic, etc , are combined with the

growth hormone Certain relatively clear-cut clinical pictures result from alteration of the growth hormone which is discussed under the heading "Clinical Manifestations of Pituitary Dysfunction"

GONADOTROPHIC HORMONE

The anterior pituitary produces two separate and distinct hormones which result in the development and maintenance of control of the activity of the ovaries and testes, and through them influences the other reproductive organs. These changes are brought about by the combined action of two separate hormones, one which acts on germ cell derivatives, and the other which affects connective tissue cell derivatives In the female, the follicle stimulating hormone is responsible for maturation of the follicles and ovulation, and in the male stimulates the seminiferous tubules The other, which acts on the connective tissue cell derivatives, is responsible in the females for lutein transformation while in the male it stimulates the interstitial cells of the testicles

Gonadotrophic hormones similar, if not identical, to these are present in the urine of some women after menopause (predominantly the follicle-stimulating hormone) and in the urine and body fluids of pregnant women (predominantly the luteinizing hormone) The gonadotrophic effects of the antuitary can therefore be produced by the combined action of extracts of menopause urine and of pregnancy urine The menopause-urine (or castrate urine) gonadotrophic factor, which is found also in the urine in under-function of the ovaries from any cause, is produced in the antuitary, probably by the basophil cells Increased amounts are found in the basophil cells after castration Injection of this menopause-urine factor into male rats (previously pituitectomized to exclude direct pituitary effects) causes stimulation of the germinal epithelium (seminiferous tubules) but not of the interstitial cells of the testis or of the accessory sex organs In the female the menopause-urine factor is chiefly follicle-stimulating, promoting development of the germ cell, hence it is gametogenic in both sexes Menopause-urine (or castrate-urine) gonadotrophic hormone stimulates the growth of the graffian follicle but without ever transforming it into a corpus luteum Some extracts of the antuitary itself have these effects, others resemble pregnancy urine in that they act chiefly on the interstitial cells and accessory sex organs

It is believed that the pregnancy-urine gonadotrophic factor is produced not by the antuitary but by the chorionic tissue of the placenta, for this luteinizing hormone is present in large amounts in all types of chorionic-tissue growths, such as hydatidiform mole and chorion-

epithelioma, whether in women or in men It is designated as the chorionic gonadotrophic hormone This chorionic hormone affects predominantly the interstitial cells and through them, the accessory sex organs Extract of pregnancy urine does not cause follicle growth when injected into pituitectomized rats It does produce a pronounced luteoid transformation of the theca cells of the follicles, and also, if there are follicles of a size sufficient to be acted upon, true corpus luteum formation In males, whether normal or pituitectomized, the pregnancy urine extract produces an extensive interstitial cell hypertrophy, but for some reason it also causes stimulation of the seminiferous epithelium Extracts of mare's serum from the midperiod of pregnancy produces in females (whether normal or pituitectomized) both follicle growth and luteinization it likewise stimulates both the seminiferous tubules and the interstitial cells of the testis This indicates that the pregnant mare's serum contains both hormones

There are three stages in the development of the graffian follicle into a corpus luteum

1 Follicles in immature ovaries These do not respond to antuitary hormone they do respond to pregnancy urine extract but only by undergoing theca lutein transformation The unresponsiveness to antuitary extract is inherent in the immature ovary tissue itself and is not due to the hormone environment, for there is no response even if the ovary is first transplanted into an adult female castrate

2 Follicles in slightly more mature ovaries, and in pituitectomized animals Maturation of the ovary proceeds to this stage of development independently of the antuitary hormones, when this stage is reached the follicle is capable of responding to the antuitary follicle stimulating factor but not to the pregnancy urine gonadotrophic hormone

3 Follicles fully developed, as found in full estrus, also in animals pituitectomized and then treated with castration urine extract or antuitary tissue This is the only state in which the pregnancy urine factor is capable of directly producing corpus luteum formation It seems therefore that the "luteinizing" antuitary hormone is capable of luteinizing the theca and granulosa of mature follicles, but has no effect on immature follicles

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thelium of testis) The castration urine principle is apparently of antuitary origin, the pregnancy urine principle chiefly of chorionic origin It is not known whether pregnancy urine contains also some gonadotrophic principle derived from the antuitary

In girls before puberty, small amounts of gonadotrophic hormone and little or no ovarian follicular hormone (estrogenic substance) can be detected in the blood or urine At puberty greater amounts of gonadotrophic hormone are found and are responsible for completing the development of the genitals In the adult, both gonadotrophic hormone and ovarian follicle hormone occur cyclically in the blood and urine, and there is evidence that corpus luteum hormone occurs cyclically in the urine This variation results from a corresponding cyclic activity of the antuitary Also a substance having the characteristics of testis hormone is regularly found in the urine

At the menopause the cyclic variation in the amount of gonadotrophic hormone ceases In 50 per cent of women none is found in the blood or urine after the menopause In the other 50 per cent of women the gonadotrophic hormone content of the blood is greatly increased, reaching even 500 rat units per liter, compared with a normal maximum of 25 rat units in the cyclic female This gonadotrophic hormone excreted after the menopause resembles that secreted from the antuitary itself and differs from the "antuitoid" (chorionic) gonadotrophic hormone of pregnancy urine Strangely enough, there are no apparent clinical differences between the two groups of women, that is, those in whom after the menopause gonadotrophic hormone disappears and those in whom it increases

When deficiency of gonadotrophic hormones occurs in the young it causes sexual infantilism Human infantilism is probably referable in most cases of hypoantuitarism In such cases the hypogonadism is secondary, being due entirely to a deficiency of antuitary gonadotrophic secretion (Even with normal amounts of antuitary gonadotrophic hormones present the gonads may fail to respond to them, the gonads themselves being at fault, this constitutes primary hypogonadism) Since the urine and blood normally contain both antuitary gonadotrophic hormone and ovarian (estrogenic) hormone, primary and secondary hypogonadism can often be distinguished by means of hormone determinations The secondary (i e , antuitary) type is more common yet therapy of amenorrhea with gonadotrophic hormones has been disappointing, probably because pregnancy-urine hormone, which is predominantly of the luteinizing type, has been employed instead of hormones obtained directly from the antuitary itself

Deficiency of antuitary gonadotrophic hormone in the adult may result in excessive bleeding instead of amenorrhea, for pregnancy urine extract is actually beneficial in hypertrophic endometrium with menorrhagia This apparent paradox is explained by the assumption that only the luteinizing factor is deficient in these cases, while there is an undiminished (or even increased?) amount of follicle-stimulating factor, which in the absence of the normal lutein transformation brings about a cystic condition of the follicles and the production therefore by the latter of an excessive amount of estrogenic substance The intermittently excessive amount of estrogenic substance causes endometrial proliferation and profuse bleeding The benefit obtained with the pregnancy urine gonadotrophic substance is apparently due to the fact that the latter induces luteinization of the large cystic follicles present in the ovaries in this condition thus reducing the supply of estrogenic substance.

In some cases showing exactly the same conditions in the ovaries and uterus, long continued amenorrhea occurs, possibly because the estrogenic substance is in these instances poured out from the cystic follicles continuously instead of intermittently

In pregnancy there is in the blood and urine a greatly increased amount of gonadotrophic (chiefly luteinizing) hormone but as mentioned above the latter is probably derived from the chorion and not from the antuitary The main action of pregnancy urine antuitary like ("antuitoid") substance is not true corpus luteum formation but transformation of theca cells into so-called theca lutein cells It has only a limited effect, if any on the maturing ovarian follicle or on the seminal epithelium of the testis The gonadotrophic hormone content of the urine begins to rise very early in pregnancy, and the detection of this rise in the urine constitutes the Aschheim Zondek test In extra uterine pregnancy the test is of great value because a positive test can be obtained at a very early stage of pregnancy The titre of the gonadotrophic hormone in the urine reaches a maximum at about the 4th or 5th month In the toxemias of pregnancy it attains very high levels during the last third of pregnancy

There is also an increased amount of estrogenic substance ("ovarian follicle secretion") in the blood and urine during pregnancy The rise in estrogenic substance occurs later and more gradually than that of the gonadotrophic hormone hence is less useful as a pregnancy test. It persists until birth after which the titre falls very suddenly and rapidly It is generally believed that the estrogenic substance excreted in the

urine in pregnancy is of placental origin because the ovary contains only a very small amount of the substance while the placenta, pregnancy blood and pregnancy urine contain large amounts

At birth the gonadotrophic hormone promptly disappears from the urine, though not as suddenly as the estrogenic substance If the titre continues at a high level during the puerperium, it is always an indication of retained membranes The titre also remains elevated in cases of death of the fetus with failure to expel it

Extremely high titres of gonadotrophic hormone are present in hydatidiform mole and chorionepithelioma On complete removal of the growth the hormone usually disappears rapidly If the urine remains positive after the removal of a hydatidiform mole, it should be tested every two weeks until it is negative, and then every month for three months, because malignant transformation into chorionepithelioma, which sometimes occurs as late as several months after removal of a mole, is associated with reappearance of the gonadotrophic hormone After hysterectomy for chorionepithelioma the test should become negative within a month, if positive after that time it is a certain indication of metastatic growth In cases of various other types of genital cancer, gonadotrophic hormone is frequently present in the urine

Embryonal carcinoma of the testis, and also true chorionepithelioma of the testis, which sometimes occurs, give rise to extremely large amounts of gonadotrophic hormone in the urine After extirpation of these growths the titre of gonadotrophic hormone in the urine is a dependable guide as to the presence of recurrence

ANTUITARY LACTOGENIC HORMONE

Mammary activity is due primarily to a separate and distinct hormone secreted by the antuitary This hormone is invariably necessary for lactation If pituitectomy is performed during pregnancy, lactation does not occur There is no evidence that the development of mammary tissue is assisted in the slightest degree by the antuitary lactogenic hormone The latter (also called prolactin) acts only on fully prepared mammary tissue, its effect is to initiate and excite secretion of milk

Estrogenic substance secreted by the ovary and placenta is normally the necessary antecedent stimulus which induces growth of the mammary gland it affects only the duct system and not the secretory alveolar tissue Estrogenic substance inhibits antuitary lactogenic hormone formation or activity Practically every mammary gland, of both male and female is exposed during fetal life and for a short time after birth to the estrogenic hormone in the maternal circulation, for in most new-

born children there is a growth spurt of the mammary glands After the estrogenic substance has been eliminated during the first week of life, the withdrawal of its inhibiting effect on antuitary lactogenic hormone often leads to a temporary mammary secretion induced by the latter

The cyclic breast changes which occur with the menstrual periods with even secretion at times, are best explained by cyclic secretion of lactogenic hormone by the antuitary That stimulation by estrogenic hormone is not invariably necessary is evident from the fact that mammary growth and lactation may occur even after ovariectomy or even after the menopause Possibly in such cases estrogenic substance is no longer required because its action upon the breast over a period of years has had some sort of cumulative or permanent effect Suckling stimulates lactogenic hormone secretion by initiating sensory nerve impulses which ultimately reach and act upon the antuitary

Unduly prolonged lactation, and parenchymal hypertrophy of the breast (or even lactation) occurring after the menopause are probably caused by hypersecretion of antuitary lactogenic hormone, or may represent a lactogenic hormone effect resulting on removal of the inhibiting action of the ovarian estrogenic substance

The corpus luteum hormone (progesterone) is the hormone characteristic of pregnancy, yet it seems to have no relation to mammary activity Likewise the fetus plays no important rôle in the physiology of the breast The placenta affects breast activity only indirectly through the estrogenic and gonadotrophic hormones secreted by the chorion The ovary is not essential to the development of the breast during pregnancy, the puerperium and subsequent lactation, for these may proceed normally following ovariectomy It appears that in pregnancy estrogenic substance of chorionic origin can be used instead of ovarian estrogenic substance for inducing breast growth in preparation for the action of antuitary lactogenic hormone While pregnancy continues, the placental estrogenic substance inhibits the secretion of lactogenic hormone, by the antuitary On expulsion of the placenta this inhibiting factor is eliminated and lactogenic hormone is secreted and brings about lactation Failure of lactation after parturition may be due to excess of chorionic estrogenic substance (delay in its elimination, or its continued production by retained membranes) or to an insufficient amount of antuitary lactogenic hormone

Gynecomastia is not understood as yet in terms of estrogenic substance and lactogenic hormone However, it often occurs in association with testicular tumors known to secrete estrogenic substance, it also occurs with pituitary, adrenal and pineal tumors Pituitary dysfunction

rarely manifests itself with respect to a single hormone This explains why mammary disturbances such as abnormal hyperplasia with or without lactation sometimes occur in cases of gigantism or acromegaly in either sex In such instances at least two of the established antuitary hormones are in excess

Animal experiments seem to suggest that abnormal duct or nipple growth may result from excess estrogenic substance alone, and that abnormal alveolar hyperplasia may result from preliminary (transitory) stimulation by estrogenic substance followed by the action of antuitary lactogenic hormone In cases of the latter type characterized by lobular hyperplasia, some regression of the overgrowth has been obtained by the injection of estrogenic substance, which presumably acted upon the antuitary to inhibit secretion of lactogenic hormone Fibroadenoma has been partly reproduced in the male monkey by injections of estrogenic substance and lactogenic hormone The growth of mammary tumors is accelerated by pituitary extracts

Simultaneous assays of the blood and urine for estrogenic substance, lactogenic hormone and gonadotrophic hormone should be of aid in the understanding of mammary conditions However, convenient tests for lactogenic hormone are not available at present Antuitary lactogenic hormone given 6 days postpartum to women in whom lactation had failed to develop has brought about lactation in most cases and no adverse effects have been noted

ANTUITARY THYROTROPHIC HORMONE

Administration of adequate amounts of antuitary extracts to normal animals results in enlargement and hyperplasia of the thyroids within a few days Increased thyroid activity is evidenced by rise in metabolic rate and heart rate, exophthalmos, decrease in the iodine content of the thyroid and increase in the iodine content of the blood In normal individuals the average maximum increase in metabolic rate obtainable in this manner is 26 per cent, but in animals having a subnormal metabolic rate, the increase is much greater The thyroid-stimulating hormone acts only in the presence of the thyroid, complete thyroidectomy obliterates all of its specific effects Following thyroidectomy in animals enlargement of the pituitary occurs A close relation between the pituitary and the thyroid has also been observed clinically Patients with hypopituitary conditions frequently have a subnormal basal metabolic rate, and their thyroid is often small and sclerotic

Pituitectomy is invariably followed by hypothyroidism The thyroid suffers atrophy and the metabolic rate falls to about 75 per cent of

normal These animals are much more sensitive to thyrotrophic hormone than normal animals Subnormal functioning of the antuitary from any cause may lead to hypothyroidism

Paradoxically, high titres of thyrotrophic hormone are reported in myxedema, and low titres in exophthalmic goiter Possibly an antithyrotrophic hormone accounts for the latter finding Or it may be explained by thyroxine having a counteracting effect on thyrotrophic hormone, or perhaps the overacting thyroid gland uses up so much thyrotrophic hormone that the blood titre is low

The thyrotrophic hormone is not active when taken by mouth, it is destroyed by boiling A satisfactory convenient test for the hormone is not available After injections of thyrotrophic hormone over long periods of time there occurs a decrease in the size of the thyroid and in the metabolic rate This loss of response is believed by some to be due to a specific inhibitory substance (antihormone) in the blood

ANTERIOR PITUITARY ADRENOCORTICOTROPHIC HORMONE

Since there is a rather intensive section on the adrenal cortex concerning the influence of the adrenocorticotrophic hormone, the reader is referred to this portion in order to avoid repetition

POSTERIOR PITUITARY

The posterior lobe of the pituitary is composed of pituicytes, neuroglial cells and nerve fibers None of these structures has the appearance of a secreting element except perhaps the pituicytes The postuitary secretion seems to enter directly into the general blood circulation, for none is found in the cerebrospinal fluid Two fractions, fairly highly purified have been separated from extracts of the postuitary, namely, vasopressin and oxytocin ("pitressin" and "pitocin") Neither of these substances can be prepared entirely free of the other Both cause hyperglycemia and act as antagonists to insulin

VASOPRESSIN (PITRESSIN)

Vasopressin in the therapeutic doses causes in man cutaneous vasoconstriction sufficient to produce marked pallor, but does not cause any significant rise in blood pressure Large doses may cause a fall in blood pressure due presumably to constriction of the coronary vessels It decreases the rate and minute output of the heart and the oxygen consumption of the body Repeated doses give lessened responses, tolerance is easily acquired Possibly the pressor component of vasopressin

is physiologically a factor in the regulation of capillary contractility Vasopressin stimulates contraction of the intestine This action is not present in oxytocin

Therapeutic doses of vasopressin cause a marked decrease in urine output lasting some hours in normal persons who have ingested a large volume of water, and in patients with diabetes insipidus This effect is from a direct action upon the kidney, probably increasing the reabsorption of water by certain cells of the tubules

OXYTOCIN ("PITOCIN")

Oxytocin causes contractions of the uterus Its effect varies according to the species of animal, the phase of the menstrual or estrous cycle, the presence or absence of pregnancy and the stage of pregnancy—early, late, parturition, or puerperium The response to oxytocin is affected markedly by the ovarian, placental or antuitary hormones active at the time of injection Early in pregnancy the human uterus does not respond to oxytocin by contracting, probably because of the inhibiting effect of corpus luteum hormone As pregnancy advances and estrogenic hormone increases in amount it renders the uterus more reactive to pitocin In the puerperium the uterus shows little or no response to oxytocin

CLINICAL MANIFESTATIONS OF PITUITARY DYSFUNCTION

The clinical syndromes associated with altered function of the pituitary gland may result from increased secretory activity, decreased secretory activity, or by local damage to adjacent structures The resultant syndromes may be due solely to the overactivity of the chromophil elements as seen in the basophilic and eosinophilic adenomas, they may be due to atrophy of these elements, or may result solely from pressure on adjacent structures, as in cases of chromophobe adenomas and craniopharyngeomas The age of the patient at the time the pituitary dysfunction occurs plays a prominent role in the ultimate clinical picture

GIGANTISM

This clinical picture, thought to result from an overactivity in the anterior pituitary, particularly the acidophilic cells results in an excess secretion of the somatotrophic hormones, occurring prior to the time of ossification and manifesting marked changes in growth There is a general overgrowth of the entire skeleton and the patient may become enormous in size

ACROMEGALY

This condition, also attributed to overactivity of the acidophilic cells of the anterior pituitary, results in an overgrowth of the bones of the face, hands, and feet, and occurs when the dysfunction of the normal pituitary function takes place after full skeletal growth has been reached Gigantism and acromegaly may co exist in those individuals in whom the pituitary dysfunction becomes manifest at the time of adolescence Both acromegaly and gigantism are felt to be the results of adenomatous tumors of the eosinophilic elements

CUSHING S SYNDROME

Considerable discussion and a description of cases with Cushing's syndrome have been elaborated upon under the heading "Hyperfunc tion of the Adrenal Cortex" It has been felt that the term "Cushing's disease" should be limited solely to those patients manifesting the clas sical syndrome as described by Cushing but exhibiting a basophilic type of adenoma of the anterior pituitary gland The question as to whether Cushing s syndrome primarily is pituitary or adrenal-cortical disease is still unanswered, but since the original description inferred that a basophilic adenoma was the sole cause of the rather clear-cut clinical picture it must suffice to say at this time that even though the pitui tary may not be the sole cause definite changes do occur in this organ even when it is shown that the adrenal cortex is probably the underlying cause

DWARFISM

This appears to be the antithesis of gigantism, and is manifest by arrested skeletal development, resulting from an insufficiency of the growth hormone, and is sometimes referred to as the Lorain type of infantilism Here again the age of onset plays a major role in the final clinical picture, in that a decrease of eosinophilic growth hormone secretions occurs before full growth is obtained, and hence results in arrested skeletal development

ACROMICRIA

This condition bears the same relationship to dwarfism as acromegaly does to gigantism. When pituitary growth hormone deficiency output occurs after full growth has been attained, there results a reduction in the size of the bones of the face and extremities which become quite delicate It is felt to be due to deficiency of a hormone of the acidophilic cells occurring after full growth has been attained

PITUITARY CACHEXIA (SIMMONDS' DISEASE)

This condition, which is characterized by mental deterioration, muscular weakness, generalized atrophy, emaciation, and ultimate death, is felt to be due to a degeneration of the anterior lobe It is known that the growth hormone is of no benefit to these patients One may speculate that this disease may be due to a basophilic element dysfunction, but there is no assurance that this is not merely a theoretical assumption It may be almost impossible to distinguish pituitary cachexia from severe anorexia nervosa, particularly when the latter has become so severe as to give rise to amenorrhea Amenorrhea is an early manifestation of Simmonds' disease but is more of a secondary later development in anorexia nervosa

DYSTROPHIA ADIPOSA-GENITALIS

This is a condition manifest by obesity, sexual infantilism, and dwarfism, and known as Frohlich's syndrome It is thought to be a lesion of the anterior lobe of the pituitary, accounting for the sexual immaturity and dwarfism But, since obesity is a feature of certain hypothalamic diseases, it is felt that there is also hypothalamic or posterior pituitary involvement as well as dysfunction of the anterior lobe The disease appears in the pre-pubertal and the adult forms, according to age when it develops Diabetes insipidus is frequently seen in these patients Pressure from tumors, or as a result from infectious disease involvement, appear to be the etiological agents The younger the age of the child at the time of development of the disease results in a greater degree of stunting, and the obesity appears more marked

In the adult type, the changes are somewhat feminizing with a tremendous amount of excess fat, which has a female distribution, loss of hair, and small tapering hands It is not unusual to see the adult type of dystrophia adiposa-genitalis give rise to obesity to the extent that the patient may weigh well over 300 pounds This condition may be confused with the Laurence-Biedle-Moon syndrome which used to be thought to be due to pituitary deficiency, but is now believed to result from involvement of the hypothalamus These patients in addition to obesity and sexual infantilism usually present a retinitis pigmentosa, polydactylism, mental deficiency, and a familial tendency

DIABETES INSIPIDUS

This condition has been ascribed to posterior lobe deficiency since it is relieved by injections of Pituitin The condition frequently accompanies tumors of the pituitary or hypothalamic regions, and is manifest

by the daily excretion of large quantities of urine of low specific gravity and low chloride content

It is interesting that total hypophysectomy will not result or give rise to diabetes insipidus and it has been postulated that there must be some secretion of the anterior lobe which antagonizes the posterior pituitary anti-diuretic factors Animal experimentations have revealed that total hypophysectomy does not result in diabetes insipidus, whereas this condition was invariably induced by removal of the posterior lobe alone Pituitin is the only available means for control of diabetes in sipidus and is not always successful

POSTERIOR PITUITARY HYPERACTIVITY

There is apparently no clinical syndrome which results from over activity of the posterior lobe of the pituitary

SURGERY OF THE PITUITARY GLAND

Many problems remain yet to be overcome before surgical management of tumors of the pituitary gland can make much progress The problem of pituitary grafting is of primary importance because if a human graft would remain functional under certain conditions, it would be possible to carry out total removal of tumors and other lesions without facing the danger of severe complications and death Professor Paul Martin of Brussels recently acknowledged that enormous advances had been made in the past few decades in regards to surgery of the ductless glands, but in the case of pituitary surgery in comparison with surgery of the thyroid, we are still at the stage where one operated only when there was a descending goiter involving the trachea and seriously threatening to suffocate the patient

THE PINEAL BODY

The structure of this body seems to be the only basis for suggesting the possibility that it may possess some endocrine function

The pineal body or epiphysis is a small cone-shaped structure arising as a diverticulum of the roof of the third ventricle A mass of cells later replaces the cavity These parenchymal and neurological cells appear to have a pseudo-alveolar arrangement.

It has been indicated that the pineal body may influence sex, growth and racial characteristics but there is no real proof In fact, the experi mental results are so equivocal that much doubt exists regarding the possession by the pineal of any physiological activity The secrets of the pineal body are thus far completely unanswered

THE GONADS

The gonads—testes and ovaries—have a close relationship with the adrenal cortex This relationship appears to be under the control of the anterior pituitary gland

THE TESTES

The urine of adult males regularly contains 1 to 8 capon units of testis hormone per liter It has been demonstrated in the urine up to the 91st year How early in life the testis begins to secrete its hormone is not known The hormone is not found in the urine of boys under 10 years of age If stimulated by gonadotrophic hormone the testes are capable of secreting their hormone much earlier than they normally do This is evident from the occurrence of precocious puberty in boys when any disturbance causes premature stimulation to the testis

No cyclical variation in gonadotrophic hormone production has been found in the male There is no increase or disappearance even in extreme old age, such as occurs in women after the menopause Estrogenic substance is regularly present in the urine (10 to 200 mouse units per liter), and sometimes in the blood of normal males

With regard to the secretion of testis hormone in constant breeders, e g , rat, guinea-pig and man, there is continuous testicular secretion throughout the reproductive period of life The extent to which the secretion of testis hormone in the urine fluctuates in this group is not known The secretion of testis hormone is influenced by nutritional conditions, the later probably act on the antuitary and through the latter affect the testis indirectly General inanition and particularly deficiency of vitamin B reduce or abolish secretion of the testis hormone

The function of the sex hormones is the conditioning of the accessory reproductive organs to deal with the germ cells in a manner to insure their proper union and the conditioning of the animal to respond characteristically so as to insure propagation of the race In higher species the psychic responses are not under the exclusive influence of the hormones They involve many factors and the relative importance of testis hormone in inducing particular psychic states is undetermined

Information is lacking as to the amount of testis hormone usually required by a normal man, or the amount which it would be necessary to inject daily for replacement therapy in a castrated man The amount excreted in the urine in 24 hours is known, its relation to the amount produced is not known There is no storage of testis hormone in the body, hence administration daily of a suitable quantity is required in order to maintain the accessory reproductive organs in a normal state Some

genital structures have a lower threshold of response to the hormone than others, e g , the prostate requires only one-third to one half as much as the seminal vesicles

Extirpation of both testicles before puberty causes (1) arrested development of the rest of the reproductive apparatus including the prostate and seminal vesicles, and failure of the mental and physical sex characteristics to appear, (2) metabolic changes, manifested by a tendency to gigantism, and an abnormal distribution of fat, (3) delay of the atrophy of the thymus which normally occurs at puberty Castration after puberty causes very similar effects in that no skeletal changes occur and the penis does not atrophy

Testis hormone stimulates the accessory reproductive organs, but it does not stimulate the testes themselves in fact, it depresses them No ductless gland is stimulated by its own secretion (Some duct glands are stimulated by their own secretion e g , the liver) When testis hormone is injected into young normal males it impairs growth of the testes and causes degenerative changes in the seminiferous tubules The injury is probably brought about indirectly, the injected testis hormone depressing the antuitary so that it does not furnish the normal supply of gonadotrophic hormone Therefore in hypogonadism with some testis tissues remaining gonadotrophic hormone is indicated, not testis hormone, for the latter would depress the remaining gonad tissue Therapy with testis hormone would be indicated in individuals suffering castration before puberty in these it would promote the development of signs of sexual maturity

In cryptorchidism or non-descent of the testis, the interstitial cells are usually hypertrophied while the seminiferous tubules usually, but not always, remain infantile and spermatozoa do not develop This non development has been thought to be due to pressure or to higher temperature within the abdomen, but it is now generally considered the result of the same congenital factor which causes the nondescent, probably deficiency of antuitary gonadotrophic hormone (gametotropic fraction) Bilateral cryptorchidism usually causes sterility, but the sex characteristics are otherwise normal Undescended testes secrete normal amounts of testis hormone

Ligation of the vas deferens in man for purposes of rejuvenation has been practiced in the belief that due to the operation the germinal epithelium undergoes atrophy and the interstitial cells hypertrophy and secrete a larger amount of hormone, but there is no available evidence that more hormone is secreted nor that the testis hormone has a rejuvenating effect on the organism

In certain organic diseases in the male there are characteristic hormone changes In malignant tumors of the testicle gonadotrophic hormone is greatly increased in the urine, the amount varying from 50 to 40,000 mouse units per liter The highest values are found in cases of embryonal adenocarcinoma, next highest in embryonal carcinoma with lymphoid stroma and the lowest values (400 to 2000 mouse units) in seminoma Metastases increase the amount excreted In chorionepithelioma of the testis the urine gives a strong pregnancy reaction, containing from 1000 to 10,000 rabbit units of antuitoid (chorionic) gonadotrophic hormone per liter and 25 to 250 mouse units of estrogenic substance per liter, the blood is negative for estrogenic substance Male breast tumors have a high content of estrogenic substance Gynecomastia is perhaps due to excess of estrogenic substance or of antuitary gonadotrophic hormone.

In contrast with these organic diseases, little correlation between male functional disease and changes in hormone balance has been found

The theories as to the cause of enlargement of the prostate gland are conflicting and confusing, as well as inadequate A hormonal imbalance seems to be a probable factor, but there is at present insufficient knowledge for rational endocrine therapy for the condition For patients with carcinoma of the prostate, Huggins of Chicago has advocated castration This appears to have some true value in reducing the course of the disease

THE OVARIES

The internal secretory functions of the ovary are

1 Regulation (not initiation) of the pubertal changes
2 Maintenance of the normal state of the other sex organs and of the secondary characters, including the mammary gland
3 Control of menstruation

It is probable, but not certain, that the interstitial cells are at least partly responsible for these functions, but the chief ovarian hormone is apparently secreted by the cells of the graafian follicle When the ovarian follicle becomes transformed into the corpus luteum the latter continues to secrete follicular hormone (at least in the human), but in addition secretes its own characteristic hormone, progestin, whose action is to induce premenstrual endometrial secretion Both ripening of follicles with consequent secretion of follicular hormone (estrogenic hormone) and corpus luteum formation with consequent secretion of corpus luteum hormone (progestin) result from the action of antuitary gonadotrophic hormones upon the ovary Much of this has been referred to under the section on "The Anterior Pituitary Gland"

OVARIAN FOLLICULAR HORMONE

Follicular hormone is present in both the blood and the urine of normal menstruating women The amount varies at different times in the menstrual cycle, there are two periods of increase, one at or near the time of ovulation, that is, about the 14th day, and a second peak about the 21st day, after which there is a precipitous drop in excretion The onset of menstruation follows this sudden reduction in the urinary content of follicular hormone There is little or no storage of follicular hormone in the body

For both gonadotrophic hormone and ovarian follicle hormone the maximum concentration in the blood and the renal excretory threshold appear to be fixed and very delicately balanced Menstrual blood contains five or six times as much estrogenic substance as does the circulating blood The active principle secreted by the growing ovarian follicle is found also in the placenta, in amniotic fluid and in pregnancy urine

The ovarian follicular hormone affects the endometrium causing hyperemia and growth, with the appearance of large numbers of mitotic figures, it does not however induce secretion or progestational changes

The immediate cause of actual menstrual bleeding is believed to be the abrupt decrease of follicular hormone causing partial destruction of the endometrium with resultant hemorrhage Experimentally, drops in the blood content of estrogenic substance can produce certain non menstrual types of uterine bleeding Large doses long continued have produced certain types of abnormal endometrium Most investigators believe that follicular hormone is responsible for the normal rhythmic contractility of the uterine musculature and that it causes secretion by the cells of the tubal mucosa

Follicular hormone does not stimulate development of the ovaries, in fact it opposes the secretion of gonadotrophic hormones by the antuitary, and hence depresses ovarian function Follicular hormone exerts in the intact animal a depressant action on antuitary functions generally, including growth inducing lactogenic and diabetogenic functions Castration on the contrary leads to an increased content of gonadotrophic hormone in the antuitary, follicular hormone administered to the castrated animal prevents this antuitary stimulation

Growth of the mammary glands is primarily dependent on follicular hormone even the male mammary gland responds to it. In male mice treatment with follicular hormone has produced mammary development in some cases localized lobular formations occurred and in other instances cancer followed

In chronic mastitis of the nodular painful type some degree of ovar

ian hormone activity is a necessary factor However, no specific type of ovarian dysfunction, either hypo or hyper, is in constant relation with chronic mastitis, and no one type of antuitary abnormality exists Possibly a vasomotor disturbance based on abnormal nervous stimuli may explain many of the clinical aspects of the condition

The content of follicular hormone in the blood remains unchanged until about the eighth week of pregnancy, when it rises from a normal of 25 mouse units per liter to 50 mouse units It remains at 50 until term The follicular hormone concentration in the urine increases gradually after the first week of pregnancy and may reach 20,000 mouse units per liter Amniotic fluid contains considerable amounts of follicular hormone Fetal blood and urine contain follicular hormone for a few days in both sexes

The enlargement of the birth canal is partly due to follicular hormone, the predominating factor however is corpus luteum hormone Both substances can perhaps be produced by the placenta since enlargement of the birth canal occurs even after ovariectomy has been performed during the pregnancy As in the case of the testis hormone there is considerable variation in the concentration of follicular hormone required to produce its different effects The least amount is required for the vaginal reactions, more for the uterine effects and a still larger amount to induce the mating reactions

After completion of the normal menopause, follicular hormone is no longer present in the blood or urine It may, however, be found in the blood and urine as long as one to two years after the onset of the menopause It is often present in cases of temporary amenorrhea in younger women and is then of help in diagnosis from premature menopause

Reliable data are not available as to the effects of extirpation of both ovaries before puberty in the human Removal of both ovaries after puberty causes more or less atrophy of the whole genital apparatus Menstruation ceases permanently The breasts shrink due to atrophy of the glandular tissue, or may become enlarged due to fat deposition The emotional disturbances produced are quite variable, they may be negligible or very severe Experimentally, ovarian grafts may function normally for a year, ovulation occurring regularly, but they eventually degenerate

Disturbances of the supply of ovarian follicular hormone have been observed in association with certain genital functional abnormalities (for example precocious development in girls, or re-establishment of menses after the menopause) and also with certain tumor growths, especially of the genital organs Granulosa-cell tumors of the ovaries

secrete large amounts of estrogenic hormone Cystic ovaries are consistently found associated with fibroids and with endometrial hypertrophy The latter may perhaps be due to hyperovarian secretion

Therapeutic applications of estrogenic hormones are not clearly defined Menopausal vasomotor symptoms when severe enough to require treatment constitute the most widespread indication for estrogenic substance therapy, which is of real though variable value in these cases This is true of both natural and artificial (surgical and radiation) menopause

Stilbestrol, a synthetic estrogen, has been found to be effective in controlling the symptoms of natural or artificial menopause even when the substance is administered by mouth

Gonorrheal vaginitis in children is benefited by follicular hormone because it causes rapid proliferation and development of the immature vaginal epithelium and thus raises the resistance of the latter to the gonococcus The treatment has been found effective, organisms disappearing in from 10 to 30 days on the daily injection of 50 rat units Undesired effects upon the uterus and ovaries have not occurred, but transitory enlargement of the breasts has been noted occasionally

In functional uterine bleeding the use of follicular hormone is not helpful for there is generally excess of follicular hormone rather than deficiency, with deficiency of progestin Gonadotrophic hormone is of help by stimulating the ovary to supply the latter In metaplasia the most frequent responsible factor appears to be an excess of follicular hormone, hence therapy with follicular hormone is illogical

Estrogenic substance means any substance that will induce growth of the vaginal epithelium Growth of the vaginal wall of rodents is used as an indicator Estrogenic substance is therefore primarily a special growth stimulant Many sources of estrogenic substances have been found, one being the graafian follicles of the ovary

For menstruation in the human female two ovarian hormones are necessary that of the follicle (estrogenic hormone) and that of the corpus luteum (progestin), and these two must be properly balanced in amount and act in a certain sequence

Certain hydrocarbons found in tar which are able to induce cancer are closely related in chemical constitution and biological effects to estrogenic hormones some of them have also estrogenic activity Corpus luteum hormone seems to have a chemical constitution similar to that of estrogenic substance, hence it is likely that it has a similar relation to the carcinogenic compounds as the latter

The relationship between the carcinogenic and estrogenic substances

may be summarized thus

1 Some carcinogenic substances are not estrogenic
2 Some estrogenic substances are not carcinogenic
3 Some substances are both carcinogenic and estrogenic
4 There is no parallelism between the carcinogenic and estrogenic potencies of these substances and the association of the two functions seems to be fortuitous

Ovarian hormones, acting in conjunction with hereditary factors, are responsible in mice for the origin of mammary cancer, the most frequent type of tumor in that species Since ovariectomy reduces the incidence of cancer in mice, the earlier castration is performed the lower the incidence of cancer The follicular hormone (estrogenic substance) would appear to be the carcinogenic factor, rather than the corpus luteum hormone, since the follicular hormone causes proliferation of the mammary gland However, there are some indications that corpus luteum hormone is also significant Estrogenic substance in large doses has induced mammary cancer even in male mice It can, though less readily, cause cancer even in low tumor-rate strains

The demonstrated carcinogenic action of estrogenic substances is restricted to the mammary tissues, in which they normally induce growth processes This limitation of effect to the secondary sex organs is in contrast to the carcinogenic agents present in tar, which may affect a great variety of tissues Carcinomatous transformation induced by either type of substance is preceded by a preparatory stage, when this stage is established the exciting agent need no longer be applied, yet cancer will develop

The National Research Council is at present conducting an extensive investigation of the influence of estrogenic and androgenic hormones on the management of mammary carcinoma

CORPUS LUTEUM HORMONE (PROGESTERONE)

The function of corpus luteum hormone is to alter the structure and the physiological reactivity of the endometrium so that the latter will respond to contact with the embryo by forming the maternal part of the placenta The hormone is believed to act also on the uterine muscle, rendering it quiescent It perhaps is responsible for the relaxation of the symphysis pubis which occurs during pregnancy in the guinea pig, though some believe that this effect is due to a separate corpus luteum hormone, provisionally named relaxin Removal of the corpus luteum early in pregnancy causes failure of implantation of the ovum and of placenta formation, removal at a later stage causes destruction of the

pregnancy The corpus luteum hormone is called progesterone from the fact that it "favors gestation"

Though the corpus luteum acts in each menstrual cycle for about 2 weeks, bringing about premenstrual changes in the endometrium, it has no useful action except in relation to pregnancy

The corpus luteum of pregnancy is believed to be responsible for the following events

1 Cessation of ovulation and menstruation
2 Embedding of the ovum and development of the placenta
3 Enlargement of the breast

Progesterone is a crystalline hydrocarbon with formula $C_{12}H_{30}O_2$ It is inert when taken by mouth In castrated women in whom large doses of estrogenic substance have first restored the uterus to the normal interval stage, progesterone can produce premenstrual endometrial changes

There is as yet no corpus luteum therapy which has been proved to be of value

MENSTRUATION

The growth phase is physiologically the first stage of the menstrual cycle, it is induced by ovarian follicular hormone and is characterized especially by hyperemia, rapid hyperplasia and the appearance of very many mitotic figures in the endometrium The later changes in the endometrium (premenstrual or progestational) are induced by corpus luteum hormone They are not necessary antecedents of the actual hemorrhage That corpus luteum hormone is not an essential factor in the causation of menstrual hemorrhage is indicated by the fact that the latter frequently occurs without ovulation (and therefore without the presence of a corpus luteum) in normal monkeys and occasionally in women also by the fact that menstruation can be induced in monkeys and in women with follicular hormone alone Estrogenic (follicular hormone) therapy employed for the relief of operative menopause symptoms produces endometrial development which attains only the normal resting (interval) stage There is no progestational transformation The premenstrual changes in the endometrium produced by corpus luteum hormone are related more to a fertile cycle, i e, to a supervening pregnancy than to menstruation

Follicular hormone and corpus luteum hormone (progesterone) are secreted by the same cells in different phases of their life, in the opinion of some authorities In any case, they are closely related in chemical structure Secretion of both of these substances is dependent upon

normal functioning of the antuitary (production of antuitary gonadotrophic hormones).

Ovulation occurs most frequently approximately at the midpoint between two successive menses. The actual cause of ovulation is not known. It is probably neither the follicle-ripening gonadotrophic hormone nor the luteinizing gonadotrophic hormone but the combined action of delicately balanced amounts of both of these operating in proper sequence.

The primary cause of the menstrual rhythm is unknown, but a variation in the amount of gonadotrophic hormone present in the pituitary at different times in the estrus cycle of animals has been *demonstrated. Perhaps the sequence of events is as follows: The antuitary* follicle-stimulating factor brings about the secretion of follicular hormone by the ovarian follicles and then the latter reacts on the antuitary causing it to secrete the luteinizing factor. The latter, by transforming the follicles which are secreting the follicular hormone into corpora lutea, checks the production of this hormone. The resultant decrease in the concentration of follicular hormone in the blood, occurring at a time when a certain amount of endometrial growth has already been induced, is then the immediate ovarian exciting cause of menstruation.

FEMALE SEX HORMONES IN DISEASE CONDITIONS

Reduction in the amounts of gonadotrophic hormone and follicular hormone in the blood and urine is found in amenorrhea, oligomenorrhea, functional sterility and often also in dysmenorrhea. The hormonal changes found in these conditions are of help in prognosis. It is probable that in most cases of so-called primary ovarian deficiency the ovary is capable of responding to antuitary stimulation if the latter were available. There is no known way of stimulating the antuitary except by radiation, which is uncertain in its action.

After artificial (surgical or radiation) menopause follicular hormone is absent from the blood and urine, gonadotrophic hormone is increased in about 50 per cent of cases, absent in the others. The increase usually starts about 8 weeks after operation (sometimes as early as 10 days) and may persist indefinitely. Removal of the uterus with retention of the ovaries does not affect the blood or urinary cycles of gonadotrophic hormone or follicular hormone.

In overfunction of the ovaries there is a marked excess of follicular hormone in the urine, the amount in the blood remains normal or decreases. Clinically these patients have precocious puberty, pubertal

bleeding, menorrhagia or metrorrhagia Rarely, overfunction of the ovary may be present without excessive uterine bleeding, namely in the condition of so-called premenstrual tension, which is characterized by certain physical and psychic disturbances In these cases the excretion of follicular hormone is markedly diminished, the blood concentration of follicular hormone is raised to a level not found in other conditions except pregnancy These changes are thought to be due to elevation of the kidney threshold for follicular hormone

The gonadotrophic hormone concentration in the blood may be normal in overfunction of the ovaries

In fibromyoma or pelvic inflammatory disease with excessive bleeding there is no increase in the amount of follicular hormone excreted The status of gonadotrophic hormone has not been determined In ovarian tumor with precocious puberty follicular hormone is found in the urine, it disappears after removal of the growth Varying amounts of follicular hormone may be extracted from ovarian carcinoma, sarcoma and teratoma, and from adrenal carcinoma Larger amounts are recovered from chorionepithelioma, whether situated in the uterus, ovary or testis

There have been no hormone observations on patients with arrhenoblastoma, the masculinizing tumor of the ovary There is no testicular tumor which causes the development of female characteristics in men It would seem that a germ cell with female factors may give rise to male cells if, in the course of atypical cell division one sex chromosome gets lost whereas male germ cells can never turn into female cells, because the required additional chromosome is not present

After fetal death, the follicular hormone content of the blood diminishes within 24 hours Since the blood concentration of follicular hormone in pregnancy is not very high, the decrease following death of the fetus is not of assistance in diagnosis Gonadotrophic hormone persists in the urine for only a few days after death of the fetus

In all types of cases of retained placenta the pregnancy reaction (gonadotrophic hormone test) of the blood and urine remains positive

In eclampsia there is an increase in the blood of gonadotrophic hormone and also of the antidiuretic factor of the postuitary

In ectopic pregnancy the biological test determines primarily whether living chorionic epithelial tissue is present in the body A positive test in this condition therefore signifies a growing extra uterine pregnancy or one in which death of the fetus may have occurred shortly before the time of the test In the latter case the test is positive because gonadotrophic hormone is excreted as long as living chorionic tissue

persists, and that usually is for a number of days, just as occurs after death of the fetus in intra-uterine pregnancy If only Reaction 1 is found in a case of suspected ectopic pregnancy it supports the clinical diagnosis and suggests that the pregnancy has ceased to grow a short time before Usually in such instances the reaction later becomes completely negative An entirely negative test in ectopic gestation indicates that the fetus is no longer alive and that there are no chorionic villi capable of growing and eroding blood vessels

In hydatidiform mole the pregnancy test is positive The blood and urine contain very large amounts of gonadotrophic hormone, the quantity varying with the size of the mole When hydatid mole is suspected the urine should be tested quantitatively for gonadotrophic hormone With values over 100,000 mouse units per liter of urine, there is probability of a mole, but not certainty, for high values may occur in twin pregnancy

In chorionepithelioma the pregnancy test is positive and there are large amounts of gonadotrophic hormone in the urine comparable to those found in hydatid mole In hydatid mole, therefore, the urine test should be repeated every 8 to 10 days after evacuation of the uterus until it becomes negative Gonadotrophic hormone may persist for as long as two months following hydatid mole without malignancy developing, but close clinical observation is indicated in such cases If the test becomes negative following discharge of a hydatid mole and later becomes positive again it indicates probable malignant change (unless pregnancy has occurred) Recurrence of a positive test after removal of a chorionepithelioma indicates metastatic growth In any condition with a persistent negative test, chorionepithelioma can be ruled out

The Aschheim-Zondek test is not specific for pregnancy, for all tumors which contain chorionic epithelial tissue give a positive pregnancy reaction, for example teratomas in men or women, especially in the gonads Many diseases of the pituitary may give positive gonadotrophic reactions also

In the Friedman modification of the test mature female rabbits are used instead of infantile mice or rats, a positive gonadotrophic reaction is evidenced by the occurrence of rupture of mature follicles within 16 to 24 hours This test is of special value in extra-uterine pregnancy because of its speed, it may make it possible to operate two to three days earlier than with the use of the Aschheim-Zondek test In most cases, of course, no biological reaction is needed for the diagnosis of ectopic pregnancy

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Chapter XVII

THE THYROID

General Physiology of the Thyroid Gland In the developmental scale of endocrine glands the thyroid belongs to the alimentary tract. Although the gland is not essential to life, it is necessary for the maintenance of health. Normally the gland weighs 20 to 30 grams and contains about 15 milligrams of elemental iodine.

An important function of the thyroid gland is to manufacture thyroxin, the principal active iodine containing substance in the body. Considerable mystery still remains concerning the function of the thyroid gland, however, the action of its hormonal product and its interrelationship with the other endocrine organs has been established by the remarkable work of De Robertis and his colleagues between 1941 and 1946, during which time, by remarkable microcytological and microchemical tests, certain aspects of thyroid function were cleared. He stated that vacuoles in the colloid and so-called chromophobic secretions are artefacts. It was found that activation of the gland by thyroid stimulating hormone produced a great increase in intracellular colloid, which was noticeable as early as 15 minutes after the administration of the hormone. These observations indicate that the cells secrete toward the follicle, producing a type of apocrine secretion which is evident when the cells are strongly activated. Afterward, apical secretion stops and the release of colloid through the cells is observed. This increase of intracellular colloid is thought to be the most sensitive method for detecting a stimulating hormone. Because of the large size of the thyroid globulin molecule, one could not explain the release of the colloid through the cells by laws of permeability and it was suggested, therefore that an enzymatic mechanism was probably involved. In 1941, De Robertis found in colloid extracted from single follicles, proteolytic activity was increased with activation of the gland and decreased under opposite conditions. He further states that in severe toxic goiters in the human there is an increase of proteolytic activity of about 100 per cent, whereas in simple goiter it is diminished to about minus 30 per cent which would seem to indicate that the proteolytic system has an important role in the physiopathology of these diseases. Although thyroxin is the important hormone elaborated by the thyroid,

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a period of 60 to 80 days to approximately 40 to 45 per cent below normal In such a severe case of hypothyroidism, 10 milligrams of thyroxin raises the basal metabolic rate to about normal in from three to ten days and this effect will last from 70 to 80 days However, there is a period of intoxication which is characterized by muscular pain and tenderness, loss of hair, peeling of the skin, fever, and sometimes nausea and vomiting, which begins 24 to 48 hours after the injection Maximum clinical improvement is obtained in about 30 or 40 days The normal thyroid produces 0 25 to 0 35 milligrams of thyroxin daily, which corresponds to about 0 2 milligrams of iodine per day The daily requirement of iodine is about 0 2 milligrams per day The average amount taken in ordinary diet over the United States is about 1 0 milligrams per day and is, therefore, more than adequate to prevent simple goiter except in the regions of endemic goiter

Iodine is stored to a significant extent only in thyroid tissue, although a certain percentage of the dose is always distributed to all of the tissues Excretion of tagged radio-active iodine has been noted to take place gradually by way of the kidneys and a slight amount through the feces The prompt accumulation of radio-active iodine by the thyroid glands of patients with hyperthyroidism is followed by rapid loss of from 50 to 80 per cent of the labeled iodine which has been taken up during the first few minutes subsequent to the administration of the tracer dose In 1942, Hamilton pointed out that these results proved active thyroid cells to have an altered mechanism for the retention of recently deposited iodine Thus, their marked avidity for the accumulation of iodine is offset by an almost equally rapid loss Conversely, patients with hypothyroidism show a reduced capacity to concentrate iodine in the thyroid gland. This small uptake of iodine may be explained by the fact that the thyroid tissue cannot produce thyroid hormones in sufficient quantities to meet metabolic requirements

The findings of Hertz, Hamilton, Soley and others have served to confirm and substantiate theories which have been promulgated since the time of Plummer

Blood Iodine The blood iodine concentration may be an *index* of thyroid function The conclusions drawn by Salter on the metabolic fate of the thyroid hormone are that there is a continuous circulation of iodine in two named forms, namely, iodide and thyroid hormones Whether or not other forms of organically bound iodine exist normally is unknown but apparently if present they also circulate in a characteristic fashion

Inorganic Iodine Inorganic iodine is trapped and concentrated in

other substances are known to be manufactured by the gland Diiodotyrosine, levotyrosine and possibly other iodine containing compounds appear to be present in the thyroid secretion, but are of less importance as far as the conditioning of metabolic processes in the body is concerned From a study of iodine, Lebond, Mann and Warren concluded that diiodotyrosine is the precursor of thyroxin and confirmed Harington's theory on the synthesis of thyroxin

Thyroxin: As has been stated, the primary function of the thyroid gland is to manufacture iodine-containing hormones, the principal of which is thyroxin A secondary function of the thyroid gland is to store the hormones and to release them into the blood stream in appropriate quantities depending upon metabolic requirements These functions are not only dependent on the internal behavior of the thyroid parenchyma itself, but are in turn regulated by other endocrines such as the thyroid stimulating hormone of the anterior pituitary and by adrenal activity

The clinical picture of the patient with hyperthyroidism strongly suggests a close inter-relationship between the activity of the thyroid gland and the sympathetic nervous system In 1915, Kendall isolated thyroxin in crystalline form In 1927, Harington and Bergere synthetized thyroxin by combining two molecules of the amino-acid diiodotyrosine. Although the compound thyroxin is 10,000 times more active pharmacologically than diiodotyrosine, it accounts for only 30 per cent of the total iodine of whole normal thyroid The remaining 70 per cent is combined as diiodotyrosine

It is apparent that thyroxin can be manufactured outside of the thyroid gland Laboratory evidence suggests that the liver, kidneys and gonads may take over part of the function of manufacturing thyroxin after total removal of the thyroid Administration of inorganic iodine to animals subjected to total thyroidectomy will raise the basal metabolic rate and produce specific changes in the epiphysis of the long bones characteristic of thyroid action

The principal effect of thyroxin is that of its calorigenic activity, that is the oxidation of protein, fat and carbohydrate and the metabolism and excretion of certain minerals, notably calcium and magnesium The tachycardia usually observed after giving thyroxin has been found in rabbits to continue for hours even after the heart has been excised and transferred to Ringer-Locke solution Under the influence of thyroxin, cells metabolize at a faster rate resulting in increased oxygen consumption and carbon dioxide production, whereas urinary nitrogen increases Total thyroidectomy causes the metabolic rate to decline over

roidectomy, or even following nonthyroid surgery for the first 24 hours, and the daily loss may be as much as 2 0 milligrams

It has also been shown by Puppel and Curtis that normal persons on a low iodine intake excrete more iodine than they take in, and that patients with exophthalmic goiter on a low iodine intake also display this negative iodine balance, but that it is two to three times as great Feeding increased amounts of iodine produces an immediate positive balance in both normal and hyperthyroid persons, but the pronounced retention of iodine is twice as great in hyperthyroid patients as in normal persons

Lahey found some correlation between the basal metabolic rate and the blood iodine level He believes that during the first year of hyperthyroidism, the blood iodine is usually above normal and that later it falls below normal as the iodine stores of the body become exhausted and the patient clinically has more severe hyperthyroid disease and by the same token a higher recurrence rate

Following total thyroidectomy for cardiovascular disease, there is a great increase of the urinary loss of iodine for about 48 hours and the blood iodine decreases to one third its normal level The urinary loss then returns to a somewhat lowered normal level Part of the excess iodine is derived from extrathyroid tissues

The blood iodine will be increased if there is a greater intake of iodine from the digestive tract or if there is an increased output of iodine from the thyroid gland or other organs and tissues This rise will persist only if the thyroid gland, liver and other tissues are able to take up and utilize the iodine normally or under certain conditions are unable to metabolize and dispose of abnormal supplies of iodine-containing substances

The blood iodine levels, as shown by Dannowski, Winkler and others, indicate that each grain of desiccated thyroid USP effects an increase in serum iodine averaging 2 gamma per cent Winkler pointed out that, even in the complete absence of hormone production by the thyroid gland a final serum concentration of about 6 0 gamma per cent, a level close to normal, should result from the administration of three grains of desiccated thyroid daily

Hyperplasia of Iodine Deficiency If the supply of iodine through the alimentary tract is deficient, as in regions of endemic goiter, striking changes take place within the thyroid gland The first of these changes is hypertrophy and hyperplasia of the entire gland The stores of colloid are exhausted and the low cuboidal cells lining the follicles become columnar and increase in size and number The entire gland be

the thyroid gland after abstraction from plasma which is very poor in iodide There is no definite evidence that any other tissue in the body can effect so marked a concentration

The Relation of Thyroid to Iodine: Since the introduction of iodine medication as the preoperative treatment for the exophthalmic goiter by Plummer in 1922, considerable knowledge of the metabolism of iodine and its relation to the thyroid gland has been obtained The recent use of radio-active iodine in the study of the metabolism of iodine and the function of the thyroid gland has greatly facilitated the investigations, its physiology, both normal and abnormal Radio-active iodine appears to enter into the same biochemical reaction and physiological roles as does naturally occurring iodine Using the Geiger counter, which detects radiations produced by the exploding atoms within the radio-active iodine, the metabolism of iodine within the thyroid and other tissues of the body can be readily traced The radio-active isotopes which have been most extensively used are I-131 and I-130, whose half life is eight days and 12 6 hours respectively

Hertz, *et al*, in 1938, injected radio-active iodine intravenously into rabbits and found significant accumulation of the injected radio-active iodine within a few minutes within the thyroid gland Negative results were obtained with radio-active bromine demonstrating the selectivity of action of the thyroid in its accumulation of iodine In 1939, he reported that the collection of radio-active iodine by the thyroid paralleled the increase in the basal metabolic rate, the mean acinar cell height, and the weight of the thyroid gland that result from the injection of thyrotrophic hormone Hamilton and Soley, in 1939, confirmed the findings of Hertz and his associates with respect to increased uptake of iodine by the hyperplastic gland by studying patients with hyperthyroidism

The thyroid hormone is fixed in two general locations The first of these is the doubtful preferential accumulation in the anterior pituitary gland and the ovary The second is the fixation of the hormone in peripheral tissues notably the skeletal muscles The normal blood iodine concentration is 4 3 micrograms per 100 cubic centimeters of blood In hyperthyroidism, usually the blood iodine is elevated due to mobilization of iodine There is also an increased loss of iodine in the urine, feces and sweat so that iodine depletion occurs This negative balance causes a decrease in the iodine content of the thyroid gland itself Normally, the average daily loss of iodine in the urine is about 0 051 milligrams Curtis stated that there is an increased urinary loss of iodine in hyperthyroidism which becomes even greater immediately following thy-

covered exerts the usual inhibiting activity upon the anterior pituitary and checks its output of T.S.H. Albert states that administration of T.S.H. induces a marked depletion of the thyroid hormone content of the gland. Administration of thyroxin is followed by the reduction of T.S.H. content of the pituitary. These are the net effects since the concentration of hormone in a gland at any time represents the difference between the amount of hormone produced during a given time and the amount of hormone secreted during the same interval. As far as the pituitary is concerned, it is not known whether thyroxin induces a diuresis of T.S.H., diminution of T.S.H. production and secretion or some other result. It has been postulated that the general relation between the pituitary and thyroid is regarded as being reciprocal.

Rawson suggests that the increased collection of iodine by thyroids of animals previously treated with T.S.H. is independent of any direct action of the pituitary but is related to an iodine want produced by a purging of the thyroid with T.S.H. He concludes that the administration of thyroxin has also been observed to inhibit the action of the T.S.H. on the thyroid of rats in which hypophyses have been removed.

Exophthalmos. It is a well known fact that the exophthalmos is not necessarily present in the patient with thyrotoxicosis. It has been suggested that the stimulation by excess T.S.H. is a causative factor. A deficiency of thyroid secretion, either relative or absolute, combined with excess T.S.H., may be the combination of factors required to produce exophthalmos. An increase in exophthalmos frequently is found to follow thyroidectomy, the administration of thiouracil or iodine, or the development of myxedema. DeCourcy states that the majority of clinicians agree that, in many cases if exophthalmos is treated early by administration of adequate doses of desiccated thyroid the exophthalmos will diminish, and yet some patients may show only a slow improvement.

Ruedemann has pointed out that malignant exophthalmos is frequently associated with few other evidences of thyroid disease, a finding which strongly suggests that hyperthyroidism per se does not explain the clinical picture.

The Relation of the Thyroid to the Gonads. It has long been noted that enlargement of the thyroid is commonly observed at puberty, during menstruation, pregnancy and the menopause. The increased incidence of goiter during these same periods is easily correlated with the hypertrophy which occurs at these stages in life and further suggests the inter relationship between the thyroid gland and the gonads.

The ovary and pituitary stand next to the thyroid in iodine content

comes hyperplastic and enlarges, the colloid vanishes, and the iodine content of the gland is diminshed This is known as hyperplasia of iodine deficiency and represents a normal compensatory mechanism by which the thyroid attempts to maintain its output of normal hormones in the presence of deficiency of raw materials

Hyperplasia and Hypertrophy of the Thyroid Gland: Similarly hypertrophy and hyperplasia of the thyroid gland occur when a large portion of a normal thyroid is removed, as demonstrated by Marine Hyperplasia of the remnants can be prevented, however, by the administration of iodine

Physiological Changes in the Thyroid Gland: There is a definite tendency for the thyroid gland to undergo hypertrophy and hyperplasia in response to the demands such as occur at puberty, during pregnancy, and menopause and during weather changes from heat to cold The stimulus producing hyperplasia and hypertrophy, therefore, is a demand for more thyroid hormone than the gland can produce under existing conditions Compensatory hyperplasia seems to be imposed on the thyroid by the pituitary gland Thus, it cannot be accomplished when the pituitary gland has been removed and, conversely, the administration of the thyrotrophic hormone causes hyperplasia of the thyroid gland Although the relationship of the pituitary hormone to hypertrophy and hyperplasia of the thyroid in Grave's disease has been suspected it has not been proven

Relation of the Thyroid Gland to the Pituitary Gland: Normally there exists a delicate balance affecting the interactivity of the thyroid gland and the anterior pituitary In 1888, Rogowitsch demonstrated that total thyroidectomy resulted in pituitary hypertrophy in rabbits Administration of the thyroid stimulating hormone (T S H) which is elaborated by the anterior pituitary will cause characteristic changes in the thyroid similar to those seen in exophthalmic goiter, namely, increased size of the gland, loss of colloid and iodine, hyperplasia and hypertrophy, and development of irregular type follicles Thus, the exhibition of T S H in instances of hyperthyroidism resulting from hypofunction of the pituitary may be beneficial Removal of the hypophyses in animals is marked by involution of the thyroid which is seen clinically as myxedema This involution can be restored to normal or even made to hypertrophy by the injection of T S H Hyperactivity of the thyroid gland appears to cause a reduction of the output of T S H Hypoactivity of the thyroid stimulates the anterior pituitary to produce more T S H to correct the deficiency The increased amount of thyroid secretion thus produced when the proper level has been re-

Lerman has suggested that hyperfunction of the adrenal medulla may be a factor in the genesis of hyperthyroidism in the human

Hyperthyroidism Disturbances in function of the thyroid gland are classified as follows 1 Hyperfunction Diffuse goiter with hyper thyroidism (exophthalmic goiter or Graves' disease), nodular goiter with hyperthyroidism 2 Hypofunction Simple goiter, myxedema, in fant and adult types

It is important to consider exophthalmic goiter a disease not only of hyperfunction of the thyroid gland, but also related in some way to a disturbance in the function of the pituitary The exact etiology and sequence of events are not exactly clear However, comparison of the hyperfunctioning thyroid both in diffuse goiter and in nodular goiter reveals that the symptomatology, except for the eye signs, may be al most identical As a matter of fact, it may be impossible from the clini cal examination of the thyroid gland to determine whether or not it is one of diffuse goiter or one of early adenomatous changes Hyperthy-roidism is a systemic disease resulting in widespread disturbances of the entire body It has been postulated that the diencephalon, the pituitary and perhaps the hypothalamus are all involved in the production of the disease

The fact that single large adenomas may represent the only hyper functioning portion of the thyroid gland makes more difficult the proof of any single concept as to the exact etiology of the disease.

Using tracer doses of radio-iodine and checking concentration with the Geiger counter, Cope has shown that in some cases a solitary adenoma may take up most of the dose, leaving the remainder of the gland in a state almost resembling a burned out adenoma, seen in other cases where the normal gland takes up the greater part of the tracer dose

Possible causes of the increased output of thyroxin as previously stated by Nash are 1 Primary stimulation of the thyroid from with out. 2 Increased rate of removal of the thyroxin produced, the hyper function being compensatory

In toxic goiter the thyroid is poor in thyroxin, iodine and colloid, while the blood is abnormally rich in thyroxin and iodine, and the urine in iodine Correlation of the abnormal physiology and the symptoms arising in thyrotoxicosis are as follows With the increased output of thyroxin the basal metabolic rate rises in accordance with the amount of oxygen want in the overactive tissues To take care of the local need for oxygen there is an increase in cardiac rate and heart minute out

In hypothyroidism, fertility is reduced and thyroid administration tends to restore normal reproductive function Even when no definite cause can be determined, sterility and habitual abortion may respond favorably to thyroid hormone Means believes that, with the exception of true myxedema, there are, perhaps, no conditions in which the use of thyroid hormone is more important than in the treatment of sterility and habitual abortion Thyroid should be prescribed in any case of sterility not traceable to some definite cause regardless of whether the basal metabolic rate is standard or substandard

In the male, spermatogenesis has been improved and fertility increased by the administration of thyroid to patients who had many defective spermatozoa Thyroidectomy causes the anterior pituitary to produce increased amounts of T S H and also a gonadotrophic hormone and growth hormone Conversely, the administration of thyroxin depresses the production of thyrotrophic factor by the anterior pituitary and probably reduces the production of gonadotrophic hormones

The physiological influences involved in the amelioration of symptoms of dysmenorrhea are unknown, but the series of successes reported from the administration of desiccated thyroid is very impressive

Relation of the Thyroid to the Thymus: The thymus is usually hypertrophic in conditions of increased thyroid activity such as exophthalmic goiter and acromegaly. This probably signifies some type of antagonistic action between the thyroid and thymus

Relation of the Thyroid to the Adrenal Cortex: Hypertrophy of the adrenal cortex may be brought about by the administration of thyroid Moreover, doses of thyroid have been known to precipitate a crisis of adrenal failure, so-called Addisonian crisis, in patients with hyperfunction of the adrenal cortex It is suggested that the crisis in all probability is the result of increased excretion of salt as in hypothyroidism secondary to pituitary dysfunction

Desoxycorticosterone not only may counteract the calorigenic action of thyroxin, but may also hinder the enlargement of the adrenal cortex that would otherwise result from thyroid administration

Relation of the Thyroid to the Adrenal Medulla: The administration of thyroid increases the sensitivity of the human response to epinephrin, and in hyperthyroidism the same exaggerated response is characteristic, hence the Goetsch Test for hyperthyroidism It is thought that the thyroid hormone increases the irritability of the sympathetic nervous system or sensitizes the tissues innervated by it

gations on this subject require the test of time to establish the final value of the method

The Use of Thiouracil and Its Derivatives in Hyperthyroidism The administration of thiouracil and its derivatives, propylthiouracil and others, to the patient with hyperthyroidism results in depression of production of thyroxin by the thyroid gland It appears from the work of De Robertis, that the point of action of thiouracil and its derivatives is with the enzymatic mechanism and probably directly with the action of peroxidase in the iodinization of diiodotyrosine to form thyroxin By depressing the amount of thyroxin formed, the symptoms slowly abate, but it is also noteworthy that there is, at the same time, an associated hyperplasia within the gland itself

The administration of iodine either in conjunction with or at the end of the thiouracil course brings about an involution of the gland, so that the end pathologic picture is one that is seen with the gland simply treated with iodine

Studies with radio-active isotopes of iodine have shown that the thyroid gland of an individual treated with thiouracil stores very little iodine Further, the thyroxin content as a rule is extremely small The daily rate of fall or basal metabolic rate during thiouracil administration is slightly over one per cent in the diffuse hyperplastic goiter of Graves Disease and slightly less than one per cent in nodular goiter with hyperthyroidism.

Carbohydrate Metabolism of Hyperthyroidism In hyperthyroidism the increased oxidation of dextrose in the tissues leads to depletion of the glycogen stores in the body There is, therefore, an associated increased rate of absorption from the intestinal tract of glucose and of dextrose and the starches Althausen and Stockholm have shown that there is a depletion of hepatic glycogen sugar and protein resulting from the administration of thyroid or thyroxin. The onset of hyperthyroidism in diabetes often causes an exacerbation of the patient's disease

Thyroid Crisis Thyroid crisis is a severe reaction of the patient with hyperthyroidism in whom there is a marked exacerbation of the toxic signs and symptoms The onset of thyroid crisis is usually heralded by increasing pulse fever, restlessness, emotional excitement, vomiting and sometimes delirium mania and coma Buxton came to the conclusion that there seemed to be two outstanding clinical features common to all such cases 1 A progressive exacerbation of all the symptoms of thyrotoxicosis which indicate disturbances of function in each of the great body systems particularly the hepatic, renal, cardiovascular and

put To provide for the general necessity of nutrition the appetite is increased Weight loss is a reflection of the overall intake of nutrition versus the output by metabolic processes and oxidation. To increase the speed of circulation the arterioles dilate. diminishing the peripheral resistance and lowering the diastolic blood pressure. The systolic pressure remains high as a result of the increased output of each beat of the heart Flushing and warming of the skin associated with hyperidrosis is the clinical response to peripheral arteriolar dilation. Nervousness emotional instability tremor muscle weakness and fatigability all represent the disturbance in the neuromuscular overactivity. Diarrhea is regarded as a result of hypermotility of the intestinal tract due to increased circulating thyroxin

Iodine Administration in Hyperthyroidism: Iodine administration to the patient with hyperthyroidism results in marked amelioration of symptoms in most instances The diffuse goiter of Graves' Disease will respond more promptly to the administration of iodine than the nodular goiter with symptoms of thyrotoxicosis. Astwood recently pointed out that although there has been extensive work done on iodine and the mechanism of its action in Graves' Disease. we are still left without an entirely satisfactory explanation. However. the response to iodine administration remains a cardinal manifestation of the disease. The average fall in the basal metabolic rate is about 3 8 points per day in the period immediately following the administration of iodine. It should be pointed out that iodine alters neither the duration nor the direction of the progress of the disease. It merely abates the severity of the disease at the time it is being administered

Some authors believe that hyperthyroidism can be produced by iodine administration. but Means and Lerman do not feel that such has ever been conclusively demonstrated. As a matter of fact. they believe that if a patient receiving iodine is not improving the iodine should be continued and that to allow escape from iodine control at a high level of metabolism incurs serious risk of toxic reactions It follows that while the basal metabolic rate is rising surgical intervention is hazardous Therefore. one should wait. continuing the iodine until the metabolic rate is stabilized at a plateau and then perform the operation, if the rate is not at too high a level.

Radio-active Iodine Administration in Hyperthyroidism: The rapid uptake of radio-active iodine from the blood makes it possible to bring about destruction of the hyperfunctioning hyperplastic gland in part or in all by the administration of radio-active iodine. which allows a concentration of active radiation within the gland. The investi-

clude secondary anemia with which eosinophilia and basophilia may be associated The amount of circulating plasma may be diminished Serum cholesterol is found to be above normal Circulatory changes include prolongation of the circulation time, since the minute volume of the heart is markedly reduced, myxedematous infiltration of the cardiac musculature, lowered cardiac efficiency, electrocardiographic changes, and increase in the cardiac shadow

Primary anterior pituitary deficiency may produce secondary hypo thyroidism since there is insufficient stimulation of the thyroid by the thyrotrophic hormone Exophthalmos does not occur and gonadal atrophy is noted However, the condition may respond to small, carefully regulated doses of thyroid

Although mild hypofunction may be associated with simple colloid goiter, as a rule there is no demonstrable disorder of thyroid function in this condition The outstanding cause of simple goiter is iodine deficiency, either relative or absolute Usually iodine therapy prevents further enlargement, but it must be given with care since there is the risk of subsequent development of thyrotoxicosis

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central nervous systems 2 A break down in one or more of these systems as evidenced by terminal clinical signs and symptoms and the necropsy findings He concluded that the profound symptom complex designated as thyroid crisis supervenes only in those patients in whom there is a break in the chemical and physiologic compensatory processes of the individual These may result from infections, minor diagnostic and therapeutic procedures, and unwise surgical procedures Although it has been stated that crisis may be ascribed to a sudden flooding of the organism with thyroid secretion the opposite may be true, that is, a sudden deprivation of the thyroid secretion The latter would be more in keeping with the thyroid crisis seen in the patient soon after operation

Hypothyroidism Hypofunction of the thyroid gland may result in primary or secondary hypothyroidism Primary hypothyroidism results from a deficiency in circulating thyroxin due to absence or loss of secreting thyroid tissue Agenesis, atrophy, infection and subtotal thyroidectomy are the common causes of primary hypothyroidism

Cretinism Cretinism is the childhood manifestation of hypothyroidism, and is attributed to atrophy of the thyroid gland The classical manifestations are a subnormal basal metabolic rate, retarded growth, stunted physical and mental development, sluggishness, delayed bony development, delayed or abnormal dentition and constipation If a cretin remains untreated, the child develops a typical cretinoid facies and the characteristic pot-belly Administration of desiccated thyroid brings about a normal development in these patients

Myxedema Classical myxedema in the adult is most commonly seen either following infection or subtotal thyroidectomy, although certain cases of spontaneous myxedema are encountered The symptoms and signs are commonly a subnormal basal metabolic rate, mental and physical sluggishness, bradycardia, dullness of the sensorium, distended abdomen, constipation, flatulence, loss of libido, sterility, a dry, scaly, yellowish skin, loss of hair, hoarse voice and characteristic puffy appearance of the eyelids, face and hands Frequently, the patient complains of vague pains, sensitivity to cold, and fatigability Menstrual disorders are commonly manifested in the female

Typical myxedema does not occur until the basal metabolic rate falls to between minus 25 per cent and minus 40 per cent The response to administered desiccated thyroid is the guide to the diagnosis in any doubtful case

In addition to the reduction in basal metabolic rate, other physiological changes are notable Blood changes which may be encountered in-

Chapter XVIII

AFFERENT FUNCTIONS OF THE NERVOUS SYSTEM THE REFLEX ARC

AFFERENT FUNCTIONS OF THE NERVOUS SYSTEM

AFFERENT FUNCTIONS OF THE PERIPHERAL NERVES AND SPINAL CORD

Segmental Sensory Areas The sensory innervation of the body is definitely segmental in nature even though some fibers pursue a devious course to their destination On the trunk, the arrangement is quite regular In the extremities, the irregular conformation of the parts modifies the segmental pattern of the spinal nerves to such an extent that it is somewhat difficult to remember the areas corresponding to the various segments The lowest segment (5th sacral) corresponds not to the foot, but to the anal region and the tip of the coccyx, and bearing this fact in mind helps to avoid confusion

The characteristic feature in the case of the extremities is that the consecutive segments correspond not to successive levels on the limb but to successive areas down one side of the limb and up the other side

In the upper extremity, the segmental order is down the lateral side of the limb and up the medial side beginning with the 4th cervical segment on the shoulder, and ending with the second thoracic in the axilla The most distal point on the extremity (middle finger) is innervated by the 8th cervical segment

In the lower extremity, the segmental order is down the anteromedial aspect of the limb and up the posterolateral aspect beginning with the 2nd lumbar segment just below the groin and ending with the 3rd sacral in the perineum The most distal point on the lower extremity (the hallux) is innervated by the 5th lumbar segment

It may be noted that the most distal part of each extremity is supplied by the last segment of a region of the spinal cord, namely the 8th cervical for the middle finger of the upper extremity and the 5th lumbar for the great toe in the lower extremity these most distal points therefore mark the change from cervical to thoracic segments and from lumbar to sacral segments respectively, as one passes over to the op-

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It is not certain which of the different types of end organs recognized histologically are related to the various sensations There is evidence that the heat and cold spots fluctuate, that is, a given spot may be sensitive to hot or cold at one moment and insensitive to temperature a few minutes later and vice versa This finding has not been explained The temperature sense is perhaps the most reliable and "objective" of all forms of superficial sensation for clinical testing

Vibratory Sense Vibratory sensation is conveyed by practically the same tracts as joint sensibility (proprioceptive sensation), only occasionally does dissociation between them occur Both have the same significance in affections of the spinal cord and peripheral nerves

Quality of Sensation A given sensory receptor organ can, within limits, be stimulated by different kinds of stimuli, but it normally responds to only one type of stimulus because its *threshold* for one particular type of stimulus is lower than for other types For this reason quality of sensation is dependent to some extent upon the sensory receptors However, the quality of sensation depends chiefly upon the particular region of the brain which receives the afferent impulses, regardless of how the latter are excited

Each sensory brain area is always associated with the same sensation For example, whether afferent impulses in the optic nerve result from light affecting the retina, mechanical pressure on the eyeball or electrical stimulation of the exposed nerve trunk, the resultant sensory impression will always be one of vision, not of pressure or pain, because the impulses are carried to the visual area of the brain, which is capable of no other type of sensation than sight.

Arrangement of Afferent Fibers in the Spinal Cord The spinal cord receives by way of the posterior nerve roots, afferent fibers of the following five types, or modalities, which may be classified in three groups according to their anatomical arrangement within the cord

I First Group	1 Pain 2 Temperature
II. Second Group	3 Touch ("one-dimensional localization")
III. Third Group	4 Tactile Discrimination ("two-dimensional localization") 5 Position and Movement, Deep Pressure Vibration ("three-dimensional localization")

I The *first group* of fibers (pain and temperature) *immediately cross* to the opposite side of the cord quite *horizontally, the pain fibers being* more nearly horizontal than the *temperature fibers*

II The *second group of fibers (touch) cross to the opposite side of* the cord but not *immediately and horizontally they cross somewhat*

posite side of the limb In passing one's hand down one's own upper and lower extremity of the opposite side, beginning at the shoulder and the femoral triangle respectively, it will be noted that the hand seems to follow most conveniently a path which indicates in proper sequence the areas corresponding to successive segments of the spinal cord A loss of sensation corresponding to a segmental area is nearly always diagnostic of a spinal cord lesion

Functional Grouping of Afferent Neurons All of the peripheral nerves contain afferent fibers for conveying various types of sensory impulses These afferent fibers become rearranged in functional groups on entering the spinal cord, and another rearrangement takes place at the thalamus There are no purely motor nerves, for the so-called motor nerves contain some afferent fibers of "deep sensibility" (proprioceptive sensation), which convey to the central nervous system sensory impulses from muscles, tendons, ligaments, joints and periosteum, that is, from structures affected by muscle activity About 40 per cent of the fibers in a "motor" nerve are afferent fibers, whose sensory endings lie chiefly in the muscles themselves, hence the term "muscle nerve" is more appropriate than "motor nerve" Since deép sensibility is conveyed by sensory fibers contained in the motor nerves, rather than in the cutaneous nerves, it may be present in a region in which the overlying skin is anaesthetic

Classification of Afferent Impulses· There are three classes of afferent impulses

1 *Exteroceptive,* originating outside of or at the surface of the body, e g , sight, hearing, pain, touch, temperature

2 *Proprioceptive,* originating in the skeletal muscles and other deep connective structures and in the labyrinths, conveying sensations of position and motion

3 *Enteroceptive,* originating in the internal viscera and the blood vessels

Skin Sensory Receptors· There are separate spots on the skin distinct from one another for reception of the various sensations, a pain spot does not respond to change in temperature, a touch spot does not mediate pain, etc The opinion has been held by some, however, that pain can be produced by the excessive stimulation of any type of sensory endings, but this question has not been decided If special pain receptors are always required, it means that nature provides them together with their corresponding nerve fibers in such structures as the ureter and gallbladder, even though these structures may not have use for them throughout the life time of the individual

III It is because of this double route that they escape with less destruction than the other sensory fibers in hemisection of the cord On hemisection of the cord all the vertical fibers (Group III) originating on the affected side are divided, of the oblique fibers (Group II) some are divided and some are not, and of the horizontal fibers all escape (Group I)

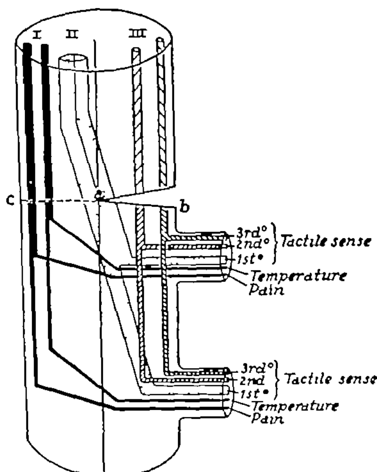


FIG 27 Sensory disturbances in hemisection of the spinal cord. The homolateral sensory loss is indicated by the line *a b* the contralateral sensory loss by the dotted line *a c*

It is obvious therefore that on the *same side* of the body as the hemisection and below the level of the latter the sensory status is as follows (1) Complete loss of tactile discrimination, deep pressure, vibratory sense and sense of position and motion—in other words, loss of proprioceptive sensation and of those qualities of the sense of touch which are closely related to proprioceptive sense (Group III) (2) Partial loss of the ordinary sense of touch (3) No loss of pain or temperature sense (Figure 27)

On the *opposite side* of the body the sensory status below the level of the lesion is just the reverse of this, namely

obliquely, sloping upward through a number of segments before they attain the other side of the cord At successively higher levels of the cord the fibers of the first two groups cross more and more obliquely At all levels they pass just in front of or behind the central canal, after crossing, they together form the spinothalamic tract in the antero-lateral white column Their ultimate destination is the cerebral cortex Cordotomy for the relief of intractable pain consists of division of this spinothalamic tract, it causes loss of both pain and temperature sense on the opposite side of the body below the level of section, but very little change in the sense of touch After bilateral cervical cordotomy, the spinothalamic tract being sectioned at the 3rd segment on one side and the 8th segment on the other, it was found by Peet, *et al*, that pain and temperature sensations were lost but that no area of total anaesthesia could be demonstrated

III. The *third group* of fibers ascend in the cord on the side on which they enter, and do not cross at all Some of them (those which do not mediate conscious sensation) form two tracts (ventral and dorsal) which ascend to the cerebellum, others form the posterior columns of Goll (the more medial column, made up of fibers from the lower segments) and of Burdach (the more lateral column, consisting of fibers from the higher segments) and pass by way of these to the gracile and cuniate nuclei of the medulla, whence they (or secondary neurons) ascend first to the thalamus and then to the cerebral cortex The functions of the fibers of this group (types 4 and 5) are to mediate conscious subjective sensations of tactile discrimination, deep pressure, vibration, position in space, and passive motion, and to enable the cerebellum, partly by means of the impulses which do not reach consciousness, to maintain posture and to coordinate muscle activity Tactile discrimination is the recognition of the distance between two stimuli applied simultaneously at different points on the surface

Hemisection of the Spinal Cord. Disturbances of Afferent Functions Functional hemisection of the cord may occur at any level due to injury, tumor (especially extramedullary) or other causes Because of the varying course in the spinal cord of the different types of afferent fibers just described, lateral hemisection of the cord causes unequal degrees of impairment of the various types of sensation

As stated above, some fibers on entering the spinal cord cross directly to the opposite side (Group I), others cross gradually and slantingly (Group II), while others do not cross at all but ascend vertically on the side on which they enter (Group III) The fibers of Group II, then, ascend partly in company with Group I and partly with Group

TABLE XXVIII

MOTOR AND SENSORY DISTURBANCES IN HEMISECTION OF THE SPINAL CORD—THE BROWN SEQUARD SYNDROME

- Brown Séquard Syndrome
  - Below Lesion
    - Same Side Below
      - Complete Motor Paralysis
      - Complete Loss
        - Proprioceptive Sense
        - Deep Touch
        - Tactile Discrimination
      - Partial Loss
        - Touch
    - Opposite Side
      - Complete Loss
        - Pain
        - Temperature
  - Zone of Lesion
    - Same Side
      - Complete Motor Paralysis
      - Complete Loss of all Sensation
    - Opposite Side
      - Complete Loss
        - Pain
        - Temperature
        - Touch

bladder disturbance in the form of retention occurs The operation diminishes bladder sensation, and it is possible that motor tracts to the bladder whose location in the cord is unknown may be damaged In the absence of pelvic disease the normal bladder function usually becomes re-established in from a few days to a few weeks After unilateral cordotomy pain sense is apt to return quickly in some cases There is evidence that some of the pain fibers do not cross but ascend in the homolateral spinothalamic tract, for Foerster has demonstrated a slight but definite decrease in the number of pain spots on the homolateral side The same is true of temperature sense fibres but to a greater degree after unilateral cordotomy there may be no demonstrable change in temperature sense on the contralateral side There seems to be a great deal of individual variation in the arrangement of the spinothalamic tracts

Saltzstein believes that subarachnoid injection of absolute alcohol (0 2 to 1 cubic centimeter) is preferable to cordotomy for the relief of intractable pain in far advanced malignant growths After alcohol injection the relief of pain lasts on the average six months [illegible] was there motor paralysis of the bladder or rectal incontinence [illegible] cases reported by Saltzstein

1 No loss of proprioceptive and allied tactile senses (Group III)
2 Partial loss of the sense of touch (Group II)
3 Complete loss of pain and temperature sense (Group I)

Since the sensory fibers of Groups I and II cross more or less obliquely in the cord, the crossing occupying in the thoracic region two or three segments and in the cervical region four or five segments, the lesion is always situated several segments higher in the cord than the upper limit of contralateral sensory loss Moreover, in the segmental arrangement of the sensory nerves of the skin there is considerable overlapping, especially from a given segment to the ones just below it This is an added reason that cord lesions are often at a somewhat higher level than the sensory changes would seem to indicate The pain and temperature sensory changes on the side opposite the lesion are somewhat more useful clinically than the homolateral disturbances of touch and muscle sense because the latter cannot be tested as easily and accurately as the former

At the same level as the lesion there is, because of coincident involvement of the roots of some of the spinal nerves, a bandlike zone of sensory loss differing from that described above In this zone on the same side as the lesion, all types of sensation are lost, because of interference with one or more spinal sensory roots, on the opposite side of the body, this zone suffers the loss of only pain, temperature and light touch sensations

The Brown-Séquard Syndrome The Brown-Séquard syndrome of functional hemisection of the cord consists of the sensory changes described above plus complete motor paralysis on the same side of the body as the lesion, below the level of the latter (Table XXVIII)

Cordotomy for Somatic Pain In 1904 Spiller observed a patient who had nearly complete loss of pain and temperature sense in the legs, but preservation of the sense of touch Necropsy revealed a solitary tubercle involving the superficial anterolateral part of the white matter of the spinal cord on the right side and another involving the corresponding fasciculus on the left, proving that this region of the cord conveys pain and temperature sensation but not the sense of touch Unilateral cordotomy for interruption of these sensory tracts can be performed as high as the second cervical segment, with removal of pain and temperature sense almost up to that level

Effects of Cordotomy In one fourth of the cases the results of cordotomy are not satisfactory Pressure sores are prone to develop because of the analgesia produced and of the usual poor state of nutrition of the subject In more than half the cases of bilateral cordotomy,

TABLE XXVIII

MOTOR AND SENSORY DISTURBANCES IN HEMISECTION OF THE SPINAL CORD—THE BROWN SÉQUARD SYNDROME

Brown Séquard Syndrome	Below Lesion	Same Side Below	Complete Motor Paralysis	
			Complete Loss	Proprioceptive Sense Deep Touch Tactile Discrimination
			Partial Loss	Touch
		Opposite Side	Complete Loss	Pain Temperature
	Zone of Lesion	Same Side	Complete Motor Paralysis	
			Complete Loss of all Sensation	
		Opposite Side	Complete Loss	Pain Temperature Touch

bladder disturbance in the form of retention occurs The operation diminishes bladder sensation, and it is possible that motor tracts to the bladder whose location in the cord is unknown may be damaged In the absence of pelvic disease the normal bladder function usually becomes re-established in from a few days to a few weeks After unilateral cordotomy pain sense is apt to return quickly in some cases There is evidence that some of the pain fibers do not cross but ascend in the homolateral spinothalamic tract, for Foerster has demonstrated a slight but definite decrease in the number of pain spots on the homolateral side The same is true of temperature sense fibres but to a greater degree, after unilateral cordotomy there may be no demonstrable change in temperature sense on the contralateral side There seems to be a great deal of individual variation in the arrangement of the spinothalamic tracts

Saltzstein believes that subarachnoid injection of absolute alcohol (0 2 to 1 cubic centimeter) is preferable to cordotomy for the relief of intractable pain in far advanced malignant growths After alcohol injection the relief of pain lasts on the average six months In no instance was there motor paralysis of the bladder or rectal incontinence in eleven cases reported by Saltzstein.

Spinal Anesthesia · Emmett points out that the literature contains very little accurate information about the physiologic events that occur in spinal anesthesia It seems that in aged persons and in those with debilitating disease the effect of spinal anesthesia is more profound and lasts longer than in younger and more vigorous patients Total dosage of the anesthetic and also its concentration in the fluid bathing the nerve roots are of paramount importance in determining the degree of nerve block that will be produced It has long been known that the various components of a mixed nerve are not equally blocked in conduction anesthesia The reason is not entirely clear, for the chemical and physical principles involved in nerve block are not understood It seems, however, that the smaller the nerve fibre the more quickly its conductivity is affected by the anesthetic solution

The sequence of nerve block in spinal anesthesia is found to be (1) sensory fibres, (2) sympathetic fibres, and (3) motor fibres Emmett gives also the following data Complete sensory effect is usually obtained in from four to eight minutes Maximal rise of surface temperature occurs within 30 minutes The time between injection and maximal motor block is quite variable, ranging from three to 23 minutes All these figures vary greatly according to the dosage and concentration used It is likely that the sympathetic fibres are actually the first to be blocked but that there is a delay in recording the effect of the indirect method which must be employed (surface temperature change) The order of recovery is (1) motor fibres, and (2) sensory and sympathetic fibres at about the same time Fractional block, that is, block of one type of nerve fibre without block of the others, can be accomplished by suitably adjusting the dose and concentration of the anesthetic agent Complete anesthesia is not necessary to secure complete vasodilatation Procaine hydrochloride 60 milligrams in 1 5 to 2 per cent solution is adequate to produce complete vasodilatation as estimated by the rise in cutaneous temperature The skin temperature is normally in a state of flux, the demonstration of a rise and then a plateau with a fairly high level (31° C or more) indicates that complete vasodilatation has been secured

Lesions of the Spinal Cord *Sensory Dissociation* While peripheral nerve or root lesions are generally followed by impairment of all forms of sensation, central affections, both spinal and cerebral, are characterized by *sensory dissociation* For example, the spinothalamic fibres entering the pons and medulla in the trigeminal nerve convey sensation from the same side of the face, hence a dorsolateral lesion in the pons or medulla causes loss of sensation on one side of the face

and of pain and temperature on the opposite half of the body (crossed anesthesia) Whenever sensation is lost on the same side of the face and body the lesion must be above the pons, that is, in the midbrain, thalamus or cortex

Intra and Extramedullary Lesions The fibres for pain and temperature sense, as they enter the spinal cord and cross, ascend in a lamellar manner The fibres from the lowermost segments are gradually pushed outward by the increasing number of fibres from the upper segments Hence in an incomplete intramedullary lesion in the cervical region, the outermost part of the spinothalamic tract is intact and as this represents the lowermost segments it will be found that the saddle area supplied by the sacral segments remains unaffected On the other hand, in an extramedullary lesion which produces compression from without, the lowermost segments are first affected, so that there is an analgesia up to, but not including, the last three or four segments below the level of the lesion

Sensory Disturbances in Cord Tumors At least 75 per cent of all spinal cord tumors are extramedullary and an equal percentage of the latter are intradural In most extramedullary tumors, and particularly those on the dorsal and lateral aspects of the cord, the greatest sensory loss occurs in the most peripheral dermatomes and the minimum sensory disturbances occur near the level of the lesion, the opposite is true of intramedullary tumors Dissociation of sensation—that is, preservation of tactile sense with loss of pain and temperature sensibility—occurs more often in intramedullary than in extramedullary tumors

Diseases of the spinal cord itself seldom cause pain or other irritative sensory symptoms, these are referable in most cases to lesions of peripheral nerves or nerve roots Cutaneous hyperesthesia and hyperalgesia associated with visceral disease may be considered irritative sensory symptoms in the sense that the noxious afferent impulses from the viscera render the somatic sensory nerves more easily excitable

Visceral Afferent Functions of the Spinal Cord and Peripheral Nerves In the above account of the afferent pathways in the spinal cord, the pain referred to is *somatic* pain, that is, pain as tested by cutaneous stimulation Within the spinal cord, *visceral afferent* impulses, in contrast to somatic impulses, pass upward not in distinct tracts but by relays of short paths with synapses in the gray matter Stimulation of the splanchnic nerve produces painful responses (visceral pain) in normal animals When, subsequently, various types of horizontal cuts are made in the spinal cord in an effort to obliterate these pain responses it is found that sections of the posterior, anterior and

lateral columns and lateral and posterior hemisections are without effect A practically complete transverse section of the cord is the only experimental lesion which is followed by cessation of these responses to painful stimulation These facts indicate that painful impulses from the viscera are conducted upward by numerous relays of short spinal neurons with synapses in the gray matter of the spinal cord, and do not traverse the lateral spinothalamic fibre tracts in the white matter which serve to transmit somatic painful impulses

Pathways for Gallbladder Pain Shrager and Ivy showed that pain responses induced by dilatation of the cystic duct could be abolished completely by section of the right splanchnic nerve and that they were unaffected by division of the vagi or left splanchnic nerves When the posterior spinal roots were sectioned it was found that if a sufficiently large number were sectioned bilaterally, the painful responses so produced could be abolished In order to intercept the pain impulses in the spinal cord, a complete transverse section of the cord, or a lateral lesion which definitely injured the gray matter, was necessary It appears therefore that visceral afferent impulses from the gallbladder pass upward through the right splanchnic nerve and the thoracic sympathetic trunk, and then by way of the rami communicantes to the spinal nerves and then by way of the posterior spinal roots into the cord Within the cord the impulses pass upward by relays of many short spinal paths with synapses in the gray matter

Cordotomy for Visceral Pain From these facts it is apparent why cordotomy operations performed for the relief of visceral pain are uniformly unsuccessful when only the spinothalamic tracts are severed Such a procedure relieves pain of somatic origin but does not relieve visceral pain When, however, the section is carried deeply in the cord so as to include a portion of the gray matter, visceral pain too is relieved It is necessary to perform cordotomy at a level several segments higher in the cord than the apparent distribution of pain, because of the anatomical fact that the pain and temperature fibres ascend many segments within the cord before they cross completely to the opposite side and ascend Posterior root sections for the relief of visceral crises are not uniformly successful, probably because of failure to section, bilaterally, a sufficient number of posterior roots

Mechanism of Visceral Pain Weiss and Davis demonstrated that subcutaneous infiltration of procaine hydrochloride solution in the peripheral area to which visceral pain is referred relieves the pain In animal experiments, the evidences of pain resulting from dilation of the cystic duct are definitely altered when cutaneous anesthesia in the pain area is produced by section of the intercostal nerves Relief of the

pain of angina pectoris by paravertebral injections of alcohol corroborates these facts, the effect probably being due at least partly to action on the intercostal peripheral nerves and not solely to injection of the sympathetic rami communicantes It is probable that visceral pain impulses produce reflexly efferent cutaneous nerve impulses, which in turn liberate a metabolite or cause some other change in the skin which is painful The somatic pain impulses thus generated are in turn carried over the usual somatic pathways into the cord and into consciousness

Visceral Afferent Pathways from the Head In the trunk and extremities the somatic and visceral afferent fibres enter the spinal cord together, so that if the posterior roots of the nerves to a region are sectioned, all types of sensation are lost In the head on the contrary, the two types of afferent fibres pursue different paths and enter the central nervous system at different levels the visceral afferent fibres of the head course downward and reach the spinal cord by way of the posterior roots of the cervical plexus, while the somatic afferent fibres run upward in the trigeminal nerve to enter the brain stem in the sensory root of the nerve Unlike other regions therefore, it is possible by posterior cervical rhizotomy to sever the visceral afferent fibres from the head region without inducing cutaneous analgesia From this circumstance the head is a peculiarly suitable region for the investigation of pain conduction with reference to the sympathetic nervous pathways

Efferent Component in Visceral Pain Stimulation of the superior cervical sympathetic ganglion produces pain in the face even after elimination of the possibility of descending afferent fibres by section of the anterior and posterior roots of the thoracic spinal nerves However, stimulation of the ganglion does not produce pain after section of the sensory root of the trigeminal nerve This suggests that the stimulation affects not afferent fibres in the sympathetic trunk which run downward to enter the spinal cord in the upper thoracic segments, but the postganglionic sympathetic *efferent* fibres so as to produce in the peripheral structures innervated by the latter some effect the exact nature of which is unknown This effect in turn causes stimulation of the ordinary somatic sensory nerve endings of the trigeminal nerve, and thus induces pain The unknown effect is possibly spasm of the blood vessels, or perhaps it consists in liberation of some metabolite. These observations indicate that relief of pain by section of sympathetic nerves is based at least partly on the interruption of *efferent* impulses There is no evidence of a visceral sensory pathway through any of the anterior spinal roots

Shoulder Pain in Abdominal Disease Shoulder pain due to abdomi

nal visceral disease ceases when the painful area is anaesthetized locally by novocaine infiltration When the phrenic nerve is exposed in the neck and stimulated by a faradic current pain is produced referred to the supraclavicular region When this area is infiltrated with novocaine subcutaneously stimulation of the nerve no longer produces pain

These facts indicate that painful impulses from the diaphragm travel over the phrenic nerves into the spinal cord by the cervical posterior roots and then descend to the upper thoracic segments, where synapse with the cells in the anterolateral column occurs Sympathetic impulses are thus initiated and pass out through the anterior roots to the cervical sympathetic chain and then are carried by postganglionic fibres to the skin These efferent impulses produce in the skin some physiological process, the nature of which is unknown This change, whatever it is, stimulates the normal sensory organs present in the skin, so that impulses travel centrally over the ordinary spinal sensory nerves into the spinal cord by way of the posterior roots, and ascend in the lateral spinothalamic tract to the brain When therefore the area of skin into which the pain is referred is anaesthetized locally, even though all other structures are intact, no pain is produced by experimental stimulation of the phrenic nerve or by disease of the diaphragm

AFFERENT FUNCTIONS OF THE CRANIAL NERVES

N I The sense of smell may be impaired by trauma or disease of the anterior cranial fossa In testing the olfactory nerve it is necessary to use substances (such as volatile oils) which stimulate the nerves of smell but not the sensory fibres of the nasal mucosa (trigeminal nerve) Unilateral anosmia is a frequent symptom of frontal lobe tumor of the brain

N II Vision is impaired in the nasal half of each retina when a pituitary tumor affects the optic chiasm, but the impairment is usually more marked in one eye than in the other A lesion of the optic tract, that is, behind the chiasm, causes loss of vision in one side of the visual field of both eyes, namely, the side opposite the lesion Around the visual center of the cerebral cortex lies a "visuo-psychic" area, located on the outer surface of the occipital lobe Its function is the recognition of the nature or "meaning" of objects seen, as distinguished from simple vision, the loss of this function results in "visual agnosia"

N V and VII In the reflex arc of the corneal reflex, the trigeminal nerve is the afferent limb, the facial nerve the efferent limb Therefore, in paralysis of one trigeminal nerve, on touching the cornea of the affected side there is no winking response in either eye, in unilateral

facial nerve paralysis there is no winking on the same side as the stimulus but consensual winking occurs on the opposite side

Ordinary sensations of the entire tongue such as touch, pain and temperature are mediated by the lingual branch of the trigeminal nerve but these fibres of general sensation, unlike the chorda tympani taste fibres with which they travel, remain with the fifth nerve all the way to and into the brain, their cell bodies are situated in the semilunar ganglion The syndrome of the auriculotemporal nerve, a branch of the mandibular division of the trigeminal nerve (N V) consists of flushing and perspiration on one side of the face on chewing foods having a pronounced taste

Pathways for Taste Impulses Impulses of the sense of taste are conveyed from the anterior two-thirds of the tongue by the chorda tympani component of the lingual branch of the trigeminal (fifth cranial) nerve, the chorda tympani as it proceeds toward the brain leaves the trigeminal nerve and joins the facial (seventh cranial) nerve, its taste fibres having their cell bodies in the geniculate ganglion of the latter and eventually ending in the facial nerve nucleus in the pons The sense of taste on the anterior two-thirds of the tongue should be investigated in every case of peripheral facial paralysis, taste is unimpaired in extra-cranial involvement, that is, after the nerve leaves the stylomastoid foramen, but is affected in intra-osseus and intracranial lesions up to the geniculate ganglion

Intravenous Tests for Taste and Smell The known methods of testing the sense of taste and smell are not entirely satisfactory The intravenous injection of certain substances elicits gustatory and olfactory sensations The intravenous method of testing smell and taste permits accurate gradation of the sensory stimulus It helps to detect differences in the capacity for olfactory perception on the two sides A water soluble camphor preparation quinine salts and several other substances have been tried by Dussik and Kauders Quinine preparations have been found particularly suitable for testing the sense of taste

Excision of the Semilunar Ganglion Removal or destruction of the semilunar ganglion e g for tic douloureux, since the ganglion contains no nerve cells of taste, would not be expected to cause any impairment of taste The fact is, however, that the sense of taste in the anterior two-thirds of the tongue is lost for several months after the operation This is probably because the resulting degeneration of fibres in the lingual branch of the fifth nerve causes swelling and therefore pressure upon the chorda tympani taste fibres contained in the same nerve interfering with conduction of taste impulses When de

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Vertigo Surgical Treatment Vertigo is a disturbance of subjective sensations with regard to the relations of the body in space It is essentially a vestibular phenomenon though the noxious stimuli affecting the vestibular centers may reach the latter from other parts of the nervous system The primary source of the stimuli may be in the gastrointestinal tract, the ocular muscles, the cerebellum, the cerebrum or elsewhere The subjective disturbances result in impairment of equilibrium Because of the spatial arrangement of the semicircular canals, vertigo is aggravated or relieved by change of position of the head Labyrinthine disease, or any lesion of the eighth cranial nerve, especially tumor of the cerebelloptine angle, is apt to cause so-called aural vertigo Menière's syndrome is not a distinct disease but a symptom complex, its actual cause is unknown Regardless of the ultimate cause, in intractable cases section of the eighth nerve through a unilateral suboccipital incision gives complete relief

Coleman and Lyerly, in a report of eleven cases, state that in no case did any attack of vertigo occur following operation, although some of the patients had slight unsteadiness, especially on sudden change of position or following quick movements This unsteadiness is not disabling and tends to improve with time Tinnitus, when not entirely abolished, was changed and improved in every case

Medical treatment of this condition has been proposed by Furstenberg Because of certain evidence that a storage of sodium in the body precipitates the attacks of vertigo, he recommends a salt free diet and the administration of ammonium chloride, 3 0 gram of the latter is given in a capsule with each meal for three successive days alternating with two day intervals during which it is withheld Talbot and Brown advise a high potassium diet (6 to 10 grams daily), instead of a low sodium diet

N IX Taste sensory impulses from the posterior one-third of the tongue are conducted by the glossopharyngeal (ninth cranial) nerve to the nucleus of the latter, their cell bodies being situated in the petrosal ganglion Taste on the posterior one-third of the tongue is difficult to examine except by the use of a weak galvanic current, which elicits normally a peculiar acid taste

Paralysis of the glossopharyngeal nerve causes anaesthesia of the upper part of the pharynx, the tonsils, fauces and posterior part of the palate and the base of the tongue, and loss of taste on the posterior one-third of the tongue, also motor impairment consisting of some difficulty in swallowing and possibly deviation of the uvula

N X Complete paralysis of the vagus causes unilateral paralysis

of the soft palate, pharynx and larynx, anesthesia of these structures and a small area of anesthesia on the anterior aspect of the external auditory meatus Unilateral interference with the visceral innervation of the vagus seems to produce no characteristic disturbances Total bilateral vagal paralysis is rapidly fatal due to respiratory obstruction from laryngealparalysis Laryngoscopic examination is necessary in every case of suspected involvement of the vagus or its nuclei

THE REFLEX ARC

DEFINITION AND CHARACTERISTICS OF A REFLEX

A reflex is a change in muscle or gland activity mediated by a reflex arc This simple definition serves to emphasize the fact that the concept of reflex action rests upon an *anatomical basis,* and discourages vague and inaccurate use of the term "reflex" in describing or explaining physiological activities Every reflex effect necessarily implies an actual neural pathway, whether long or short, simple or intricate, connecting the site of the exciting stimulus and the reacting tissue A reflex arc consists of at least two complete neurons, one afferent and one efferent, joined together by means of a *synapse* so as to form a functional unit. It is by virtue of the synapse that the reflex arc has properties differing from those of the isolated neurons Reflex actions are characterized by *localisation* of response to a given stimulus, *radiation* of response to nearby reflex arcs according to fairly definite rules of spread determined by *graded resistances* at the various synapses, and great *fatigability* as compared with the activity of single neurons

RELATION OF REFLEX ARCS TO THE CEREBRUM

Normal activity of a spinal reflex requires not only the integrity of the reflex arc but also normal functional relations between the reflex center and the cerebrum When the fibres effecting this association with the brain are destroyed by a lesion the deep reflexes are increased by reason of removal of the inhibitory influence of the brain The superficial reflexes should theoretically be similarly increased actually they are absent in such upper motor neuron lesions In explanation of this fact it is assumed that the center of the arc in the case of the superficial reflexes is in the cortex instead of the spinal cord, hence lesions even at high levels would abolish these reflexes It seems that impulses produced by cutaneous stimulation must proceed to the higher centers of the brain before they can bring about a response this view is in harmony with the fact that the primary purpose of cutaneous sensi

bility is to inform consciousness regarding the external environment Tendon sensibility, on the contrary, does not ordinarily need to reach the level of consciousness, its main purpose of coordinating the activities of the different muscles in movement and maintenance of posture can to a large extent be accomplished by reflex arcs having their centers in the spinal cord

REFLEX CENTERS

A spinal cord lesion which passes through a given segment abolishes all reflexes having their *centers* at that point The following table indicates the levels at which various reflexes have their centers

TABLE XXIX

THE LEVELS IN THE CENTRAL NERVOUS SYSTEM AT WHICH VARIOUS REFLEXES HAVE THEIR CENTERS

Deep Reflexes	*Center of Reflex*
Jaw Jerk	Pons
Triceps	C6 & 7
Biceps	C5 & 6
Wrist Jerk (Periosteal)	C7 & 8 (& 6?)
Knee Jerk	L2, 3 & 4
Achilles Jerk	L5, S1 & 2
Superficial Reflexes	
Upper Abdominal	T8 & 9
Lower Abdominal	T10 & 11
Subrapubic	T12
Cremaster	L2
Plantar	S1
Sphincter Reflexes	
Bladder & Anus	S3 & 4

PATHOLOGICAL REFLEXES

The pathological reflexes are altered types of responses, not merely quantitative changes, they occur in lesions of the upper motor neuron tracts, by reason of loss of certain obscure influences which the cerebrum normally exercises over the spinal reflex centers Exaggeration of all the deep reflexes is evidence in favor of an organic lesion only when it is accompanied by diminution or absence of the superficial reflexes and by pathological reflexes

Chapter XIX

EFFERENT FUNCTIONS OF THE NERVOUS SYSTEM CONTROL OF THE SKELETAL MUSCLE

EFFERENT FUNCTIONS OF THE NERVOUS SYSTEM

EFFERENT FUNCTIONS OF THE BRAIN

Volition and Consciousness in Movement Voluntary movement ordinarily is executed with the cooperation of consciousness, but it cannot always be clearly distinguished from "automatic" movement performed quite unconsciously or perhaps subconsciously On reflection, one can convince himself that a given purposeful coordinated movement may under different circumstances be both involuntary and unconscious, or involuntary but conscious, or voluntary but unconscious, or both involuntary but conscious And there are apparently intermediate degrees of volition and consciousness in connection with purposeful movements Fatigue seems to be more prominent, the more directly and explicitly the elements of volition and consciousness enter into a muscular activity

Occupational therapy may be considered a means of facilitating exercise of the motor apparatus by dissociating volition and consciousness from the movements performed through the introduction of other psychic factors

Pseudobulbar Palsy Bilateral lesions of the *supranuclear* pathways occur in pseudobulbar palsy, which is a clinical syndrome and not a disease entity It is characterized in the main by involvement of the tongue, lips, cheeks and throat musculature Clinically there is a certain type of disturbance (but not paralysis) of articulation, phonation, mastication, and deglutition The bulbar centers and lower reflex arcs are spared, therefore there is no lower motor neuron (flaccid) paralysis, but only loss of voluntary motor power, the functional disturbance is supranuclear in type, yet emotional activity and automatic reflex activity are preserved There is considerable weakness of the lips, cheeks tongue palate etc , but the absence of complete paralysis may be demonstrated by the reflex responses of the lips, tongue, and palate

on appropiate stimulation There is no atrophy, no muscular fibrillation and no reaction of degeneration The causative lesion in pseudobulbar palsy is numerous bilateral disease foci in various parts of the cerebral hemispheres, most often in the subcortical regions

Bulbar Palsy: Pathological foci in the bulb itself give rise to signs of bulbar palsy, which is quite different from the pseudo-bulbar syndrome In bulbar palsy, whether the nuclei or the nerve trunks be affected, the lesion is one of the *lower motor neuron,* therefore there is a flaccid paralysis of the palate, pharynx, larynx, and tongue, and occasionally also of the muscles of the lips and face The common symptoms are dysarthria and dysphagia The speech is nasal and food regurgitates through the nose Occasionally there is complete aphonia from involvement of both vocal cords Alternating hemiplegias and equilibratory and crossed sensory disturbances are frequently associated with bulbar palsy

EFFERENT FUNCTIONS OF THE CRANIAL NERVES

N III Complete paralysis of the oculomotor (third cranial) nerve causes ptosis, deviation of the eyeball laterally, dilation of the pupil, loss of pupillary reaction to light and loss of the power of accommodation In "paralysis of lateral gaze," each eye alone can move to a given side but the two eyes cannot move synchronously in the same direction Paralysis of lateral gaze is essentially a sign of an intrapontine lesion but may result from a lesion in one of several other places Also vertical nystagmus, which is uncommon, is due usually to intrapontine disease Nystagmus may be ocular, vestibular, cerebellar, or cerebral in origin

The neural disorders which can produce changes in the size of the palpebral fissure are indicated in the following table

TABLE XXX

CAUSES OF CHANGES IN THE PALPEBRAL FISSURE

Palpebral Fissure	Narrowing	Oculomotor Nerve Paralysis (N III) or Cervical Sympathetic Paralysis
	Widening	Facial Nerve (L M N) Paralysis (N VII) or Cervical Sympathetic Irritation

N V The motor root of the trigeminal (fifth cranial) nerve supplies the muscles of mastication, the mylohyoid, the anterior belly of the

digastric, the tensor tympani and the tensor palati The muscles of mastication (fifth nerve) have bilateral cortical innervation, therefore supranuclear lesions result only in weakness and not paralysis, the jaw jerk is increased In lower motor neuron lesions the jaw jerk is absent on the same side as the lesion

N VII In complete paralysis of the facial (seventh cranial) nerve there is paralysis of all the muscles of one side of the face except the levator palpebrae, which is supplied by the oculomotor nerve There fore raising the eyelid is the only movement possible, but the lid cannot be closed The corneal reflex is absent because of impairment of the motor limb of the reflex arc In nuclear (intrapontine) lesions of the facial nerve there are apt to be fibrillations, also contralateral hemi plegia may be present In supranuclear lesions only the muscles of the lower part of the face, that is from the lower eyelid downward, are in volved Anastomosis of the severed facial nerve with the spinal ac cessory nerve has been discarded partly because it may lead to the de-

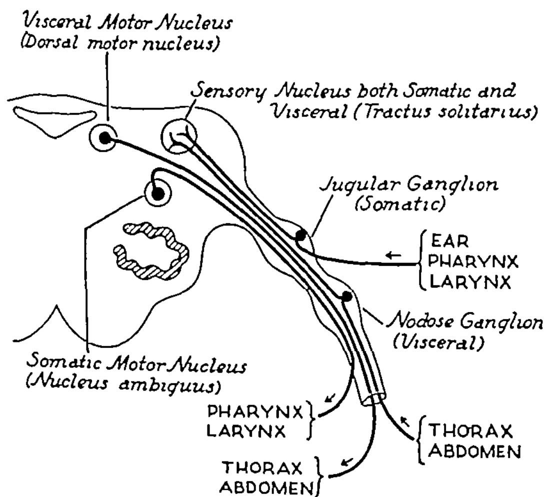


Fig. 25. Functional components of the vagus nerve and their central connections

velopment of troublesome associated spasms Anastomosis with the hypoglossal nerve may be tried but is not always successful The hypoglossal-facial nerve suture is preferable to spinal accessory-facial anastomosis because the cortical centers for the face and tongue are closer together The shoulder and facial muscle movements are not synergistic or closely associated

N IX The glossopharyngeal (ninth cranial) nerve is motor to the constrictors of the pharynx and the stylopharyngeus muscle

N X Lesions of the vagus (tenth cranial) nerve produce motor symptoms referable mainly to the larynx (voice impairment)

The vagus nerve has four different kinds of fibers, since it has both *somatic* and *visceral* and also both *motor* and *sensory* functions (Figure 28) The somatic structures to which it is motor are the striated muscles of the pharynx and larynx, it supplies sensory innervation to these same regions and also to parts of the ear The visceral structures to which the vagus is motor are the thoracic and abdominal organs, it is also sensory to these viscera The *jugular ganglion* of the vagus contains the cell bodies of the somatic sensory fibers, the *nodose ganglion* contains the cell bodies of the visceral sensory cells These two ganglia to-

TABLE XXXI

FUNCTIONAL COMPOSITION OF THE VAGUS NERVE

Vagus nerve	Somatic	Motor to	Pharynx Larynx	Nucleus Ambiguus
		Sensory to	Pharynx Larynx Ear	Jugular Ganglion ↓ Tractus Solitarius
	Visceral	Motor to	Thoracic and Abdominal Viscera	Dorsal Motor Nucleus
		Sensory to	Thoracic and Abdominal Viscera	Nodose Ganglion ↓ Tractus Solitarius

gether correspond to the posterior root ganglion of a spinal nerve Though one serves somatic and the other visceral sensation, the nerve fibers which pass from them into the medulla come together in a single sensory tract, the *tractus solitarius* The two sets of motor fibers on the contrary (somatic and visceral) have separate nuclei in the medulla, the somatic motor nucleus being situated more anteriorly (*nucleus ambiguus*) and corresponding to the anterior horn cells of the spinal cord, and the visceral motor nucleus being somewhat more posterior (*dorsal motor nucleus*) and corresponding to the sympathetic cells in the intermediolateral column of the spinal cord

Table XXXI summarizes these details

N XI The spinal accessory (eleventh cranial) nerve supplies the sternomastoid and trapezius muscles

N XII Paralysis of the hypoglossal (twelfth cranial) nerve results in paralysis of half of the tongue on the same side as the lesion. When the lesion involves the nucleus within the medulla, fibrillations occur during the process of atrophy In peripheral lesions of the nerve fibrillations are usually absent

EFFERENT FUNCTIONS OF THE SPINAL CORD AND PERIPHERAL NERVES

Segmental Innervation of the Muscles The segmental innervation of a number of skeletal muscles is indicated in the table of spinal reflexes (Table XXIX) If only a few of the motor segmental levels are kept in mind they will serve as an aid in determining the location of a given lesion For example, the biceps muscle is innervated by the sixth cervical segment, and the triceps by the seventh cervical segment. Therefore given a patient with a spinal cord lesion who can flex but is unable to extend his forearms, one may state definitely that the lesion does not extend higher than the seventh cervical segment There are many nerve fibers which lie entirely within the spinal cord, connecting the different segments

Differentiation of Spinal Cord Lesions from Cerebral Lesions Lesions in the spinal cord may produce upper motor neuron paralyses similar to those caused by lesions of the motor tracts in the brain, but differentiation is usually easy because

1 There is absence of involvement of the cranial nerves

2 The lesion and its effects are frequently bilateral because of the small size of the spinal cord

3 The associated sensory changes are often characteristic of a cord lesion

Recoverable and Non-Recoverable Lesions It is unfortunate that there are no known criteria by means of which one can differentiate clinically between a complete physiological and a complete anatomical interruption of spinal cord function The former may be a more or less rapidly recoverable lesion, but the latter is an irreparable damage from which recovery does not occur It is useless to attempt approximation or suture of the severed spinal cord because no regeneration takes place in the central nervous system The roots of the cauda equina, which have a structure similar to that of a peripheral nerve, do possess the power of regeneration

Complete Transection of the Spinal Cord 1 *Stage of Flaccidity ("Spinal Shock")* Complete transection of the spinal cord, if it occurs suddenly, is followed immediately by the condition known as "spinal shock" This is defined as the loss of all reflex activity below the level of section, occurring immediately after complete transection of the spinal cord Its cause is unknown The condition has no relation to surgical shock other than an accidental similarity in name

The period during which spinal shock persists is referred to as the stage of flaccidity Reflex tone is abolished as well as reflex movement The blood pressure falls because vasomotor pathways are severed and the peripheral resistance correspondingly decreased The flaccidity of the muscles is not due to the fall in blood pressure, for the muscles above the level of section do not become flaccid The decrease in peripheral resistance and consequent fall in blood pressure are most marked when the section is at or above the first thoracic segment, and are absent when the section is below the second lumbar, for the cord gives off all its vasoconstrictor fibers between these two levels There is a marked tendency to develop bedsores because of impairment of vasomotor reflex activity The skin is cold and blue due to the circulatory changes, and is dry due to paralysis of the sweat glands The bladder and rectum become paralyzed All sensation is lost below the level of section The stage of flaccidity is more profound and more lasting the higher the animal species in which spinal shock occurs In the frog it lasts only a number of minutes, in the monkey a few days and in man about three weeks

Since the reflex arcs below transection remain intact structurally, it is not entirely clear why the condition develops at all, the functional failure is worse than can be explained by the anatomical lesion

2 *Stage of Reflex Activity* This stage is followed by a stage of reflex activity Smooth muscle regains its reflex activity first In the urinary bladder the sphincter becomes active before the detrusor so that there is retention of urine Next the control of the blood vessels

returns due to the vasomotor center in the spinal cord developing in dependent tone, and the blood pressure rises nearly to normal Skeletal muscle reflexes are the last to recover Reflex tone returns before reflex movement, the flexor muscles regaining their tone sooner and more nearly completely than the extensors, so that the limbs assume an attitude of slight flexion Even in the flexors however, tone never becomes quite normal No wasting of muscle occurs Reflex movements of flexion of the thigh and leg appear next, associated with extension (dorsiflexion) of the foot and toes, this extension really may be considered physiological flexion since it contributes to shortening of the limb as a whole This reflex may be elicited in a number of ways, and is referred to as the Babinski, Gordon or Oppenheimer s sign according to the particular site and nature of the stimulus employed

Involuntary movements of this type often occur apparently spontaneously There is inhibition of the antagonists In man, if the response spreads to the opposite side of the body the movements are of the flexor type on both sides, whereas in animals, under the same circumstances, a "crossed-extensor" reflex occurs with flexion on the same side as the stimulus and extension on the opposite side Later on the extensor reflexes recover, but only imperfectly, the knee jerk reappears from one to five weeks later than the flexor responses, and the ankle-jerk still later Ankle clonus may develop and if so, it is of only short duration In some cases any slight stimulus below the level of the lesion induces a widespread response known as the mass-reflex, in which there are strong spasms of the flexors of the lower extremities and of the anterior abdominal muscles, evacuation of the bladder and profuse sweating below the level of the lesion The sweating involves the entire body if the cord section is at or above the first thoracic segment The coitus reflex is recovered during the stage of reflex activity The skin becomes moist again as sweating returns, and it becomes warm and its color improves as the circulation is restored by resumption of vasomotor tone and skeletal muscle activity Ulcerations begin to show a tendency to heal Reflex evacuation of the bladder and rectum is gradually established.

3 *Stage of Failure of Reflex Activity* A final stage of failure of reflex activity may set in if, as frequently happens, marked general toxemia occurs The threshold for all the reflexes is then raised and the muscles become flaccid and undergo wasting The sphincter of the bladder finally remains in a relaxed state Extensive pressure sores develop

Incomplete Transection of the Spinal Cord Incomplete transection of the spinal cord is followed by a state of spinal shock similar to

is the effect of the so-called "lengthening reaction" and "shortening reaction," and is a reflex phenomenon, that is, it depends upon functional connection of the muscles with the spinal cord Slight stretching of a tonically contracted muscle or permitting the muscle to slacken induces a movement of contraction (the "shortening reaction"), but strong stretching causes instead reflex relaxation, which constitutes the postural "lengthening reaction" In movement contraction, the tension developed is proportional to the initial length of the muscle, in postural contraction this is not the case In any complex movement some muscles are engaged only in maintenance of posture, while others execute the movement itself

"Red" and "Pale" Muscle Fibers Skeletal muscle is made up of two histologically different kinds of fibers, namely "red" fibers with poorly marked crossed striations, whose contractions are more sluggish and prolonged, and "pale" fibers with well marked striations, which are much quicker acting. It is not true, as was once supposed, that one type of fiber is for movement and one for posture, for both kinds serve the functions both of motion and of tone, besides, many intermediate types of fibers occur The fact is established that many skeletal muscle fibers receive a sympathetic nerve supply Histologically it is found that some muscle fibers receive both a cerebrospinal and a sympathetic nerve supply, others only the former In certain muscles, e g , the extrinsic eye muscles, nearly every fiber has a sympathetic supply in addition to the somatic innervation, whereas in others many fewer fibers are so supplied The suggestion has been made that the sympathetic innervation controls only the "red" fibers and regulates the tonus of the muscles but it is now known that this is not the case Division of the sympathetic supply of skeletal muscles has been said by Hunter and by Royle to decrease spasticity in certain cases of paralysis but this observation has not been confirmed Even if it were confirmed, increased blood flow due to vasomotor changes might account for the result

Sympathetic Influence on Skeletal Muscle Stimulation of the sympathetic nerve supply of resting skeletal muscle has no demonstrable effect of any kind In the case of active muscle, however, it diminishes and delays the onset of fatigue by some unknown mechanism The effect is probably not due to neutralization of products of activity if the sympathetic action on skeletal muscle is the same as that of adrenalin, for the latter increases the excitability and contractility even of resting muscle

THE PROPRIOCEPTIVE SYSTEM

Control of Muscle Tone Skeletal muscle tonus is a *proprioceptive reflex,* which is primarily dependent on the integrity of the muscle and its peripheral innervation While tonus is a reflex, it is also influenced by higher segmental mechanisms The pyramidal tract seems to inhibit tone The same appears to be true of extrapyramidal tracts, for rigidity occurs as a release phenomenon in extrapyramidal lesions The vestibular pathways seem to augment tone, for lesions of the vestibular apparatus tend to produce hypotonia Hypotonia may occur also in affections of the cerebellum, but the mechanism is not well understood

Cerebral Proprioceptive Centers The proprioceptive system of nerves for the regulation of posture and skeletal muscle tone definitely belongs to the somatic rather than the autonomic nervous system The processes involved are very complex and much remains unknown about them at present The motor centers in the higher parts of the brain down to the red nucleus in the midbrain tend to keep the muscles in normal tone and maintain the limbs in their normal positions The centers in the pons and medulla may be considered the apex of a reflex arc regulating muscle tone When allowed to act independently of the higher centers on removal of the function of the latter, they induce muscular rigidity in a somewhat exaggerated standing posture (decerebrate rigidity), the extensor (antigravity) muscles overbalancing the flexors This maintained contraction is reflex, that is, it is dependent upon a continuous flow of afferent impulses from all parts of the body, particularly from the affected muscles themselves, the state of tension stimulating sensory end organs in the muscles Such "myotatic" or stretch reflexes are more active in and more characteristic of the antigravity (extensor) muscles generally, and are less well developed in the flexors

Joint and Ligament Sensibility When a finger is anesthetized by nerve block around its base, position sense in the finger is lost, even though the sensibility of the muscles concerned is still intact Hence joint and ligamentous sensibility is a greater factor in position sense than muscle sensibility Perhaps this is due to the more varied functions of the latter in connection with maintenance of tone and mediation of stretch reflexes Joint and epiphysial cartilage is insensitive

Levels of Proprioceptive Control Transection of the spinal cord is immediately followed by complete loss of muscle tone below the level of section, after a time tone is partially regained but its distribution is altered for it is more marked in the flexors than in the extensors

Section just inferior to the red nucleus results in decerebrate rigidity, in which there is excessive muscular tonus, but only in the extensors A section higher up which leaves the connections of the midbrain and thalamus with the muscles intact does not alter the tonus in lower animals In man, however, muscle tonus is disturbed following such a lesion, for normal tonus is preserved only when the corpus striatum, a structure at a still higher level remains and the pyramidal is undisturbed The cerebellum, too, has some poorly understood influence upon posture, though it is chiefly concerned with voluntary movement Its extirpation does not abolish decerebrate rigidity

The vestibular apparatus of the internal ear is an important accessory organ of skeletal muscle control Proprioceptive and vestibular sensations may be considered the principal afferent mechanisms for the coordination of muscular activity

The Cerebellum The inferior and middle cerebellar peduncles are the main afferent tracts of the cerebellum while the superior peduncle is the efferent path, although it also contains some afferent fibers Through the peduncles the cerebellum stands in very intimate relation with the rest of the central nervous system Though it does not send fibers directly to the cerebral cortex or basal ganglia, impulses can be conveyed to them by several indirect routes It receives visual, auditory, somesthetic and kinesthetic impressions from the brain, sensory impulses from the body and limbs and vestibular impulses from the semicircular canals By means of all these afferent impulses, its association fibers, and its efferent connections with the rest of the brain and spinal cord, the cerebellum serves as the chief unconscious central coordinator of muscular activity It is termed by Sherrington "the head ganglion of the proprioceptive system"

Function of the Cerebellum · The function of the cerebellum is *synergia,* that is, the coordination of equilibratory (walking and standing) and non-equilibratory (e g , finger-to-nose test) muscular activity Synergia is the fundamental cerebellar function, and asynergia or ataxia the fundamental symptom of cerebellar disease By synergia is meant the synchronous and orderly activity of groups of muscles for the purpose of carrying out definite movements with proper coordination as to speed, amplitude and force A disturbance in the proper ratio of these elements results in dyssynergia or asynergia and shows itself in faulty attempts at correction or overcorrection, and in the breaking up or decomposition of movement Two other symptoms are generally attributed to disturbance of cerebellar function, asthenia and atonia, but it is probable that the first is primarily due to asynergia and the second only

to an indirect influence of the cerebellum Neither is a direct effect of cerebellar dysfunction

Cerebellar Fits Attacks of hypertonus ("cerebellar fits") sometimes occur in irritative lesions these are not strictly a manifestation of cerebellar dysfunction, but are better interpreted as an instance of decerebrate rigidity The cerebellar fit consists of a tonic convulsion involving all four extremities, opisthotonus and marked respiratory and vasomotor symptoms It is sudden and is accompanied by unconsciousness, cyanosis and dilated, immobile pupils, but not tongue biting or incontinence Large cerebellar lesions sometimes give rise to comparatively little ataxia Cerebellar ataxia differs from that of tabes dorsalis in that there is no loss of sensation in the former In some cases marked dyssynergia not infrequently disappears despite the fact that the cerebellar disease process is progressive This is particularly true of tumors It seems that there is considerable power of adjustment to, or compensation for, the initial dyssynergia, the cerebrum can apparently take over the function of the cerebellum to a large extent

Localization of Function in the Cerebellum There is some localization of function in the different parts of the cerebellum, comparable in a limited measure to cerebral localization Cerebellar localization however has to do with the direction of movement of limbs or parts of limbs, rather than with the movement of individual muscles Each side of the cerebellum stands in functional relation with the corresponding half of the body, thus the left lobe controls the left limbs, the right lobe the right limbs and the right and left halves of the vermis relate to the respective halves of the body (trunk) This is just the opposite of cerebral localization of function The clinical significance of these facts is that a lesion of one side of the cerebellum gives rise to symptoms on the ipsolateral half of the body Although the efferent cerebellar fibers cross to the opposite red nucleus the subsequent recrossing of the rubrospinal tract makes for ipsolateral functional control Similarly each side of the cerebellum stands in functional relation with the opposite cerebral cortex yet because of the crossing of the corticospinal (pyramidal) tract has ipsolateral influence on the musculature

DISORDERS OF MOTILITY

Classification of Motility Disorders Disturbances of motility are quantitative (positive or negative) or qualitative Paresis and paralysis are negative motor symptoms Positive or irritative motor symptoms are usually related to injury of nerve cell bodies within the central

nervous system The most common types are (a) fibrillations, (b) myoclonic contractions and (c) convulsions

Fibrillation Fibrillations are slow vermicular twitchings of individual muscle fibers or bundles They are caused chiefly by the gradual degeneration of motor cells in the anterior horns of the spinal cord They may occur sometimes in slow degenerative lesions or peripheral nerve fibers Also during regeneration of motor nerves muscle twitchings sometimes occur

Myoclonus Myoclonus is a sudden, momentary, localized, regular or irregular twitch of a muscle or part of a muscle, resembling a contraction induced by an electric shock, which usually does not produce movement of a part It is unaffected by volitional effort, is aggravated by emotion and generally disappears during sleep Hiccup is an example, it is a spasmodic myoclonus of the diaphragm

Convulsions Convulsions due to disturbances of the spinal cord, as in tetanus, are mainly tonic in type, and are reflex in that external stimuli are a necessary factor Disturbances of the cerebral motor cortex, whether due to a local lesion such as tumor or depressed skull fracture or to general toxemia, such as uremia, cause epileptiform convulsions Local cortical lesions usually are associated with the so-called Jacksonian convulsion, this is localized to a certain group of muscles or begins always in a certain group and spreads successively to adjacent muscles with a fixed order of progression, may be tonic or clonic and may or may not be accompanied by impairment of consciousness The site at which the convulsion begins is of assistance in determining the location of the lesion in the cortex

Spasm A spasm is a sudden convulsive contraction of a muscle or a group of muscles producing a movement which has no definiteness of purpose or functional pattern

Tic A tic consists of a sudden, abrupt, rapid, involuntary contraction of a muscle or group of functionally related muscles Every tic has what seems to be a functional pattern or an ideational purpose, although this may appear in exaggerated or even grotesque form The movement does not correspond to any peripheral nerve or segmental muscular distribution, but represents a function

Myotonia Myotonia is a heightened muscular irritability and contractility with lessened or slowed power of relaxation It is a symptom which may occur in a number of diseases but constitutes practically the entire clinical picture in myotonia congenita

Ataxia and Asynergia Examples of qualitative changes in motility are ataxia and asynergia There is a vast difference between a simple

contraction of a muscle and the harmonious group of movements which accomplish a given result Ataxia and asynergia are dependent upon loss of normal *afferent* regulatory impulses, as in lesions of the spinal cord (tabes) or disturbances of the *cerebellum*

The Abdominal Reflexes Physiologically the abdominal reflexes are spinal segmental reflexes of the flexor type, *augmented* by cortical activity and *inhibited* by extrapyramidal centers, therefore they are diminished in lesions of the corticospinal pathways and increased in basal ganglion disease In these respects they stand in contrast to reflexes of the extensor type, e g , the knee-jerk

Lesions of the Pons *Pontine lesions* are characterized by the "superior type of alternating hemiplegia," consisting of internal strabismus (from paralysis of the external rectus of the eyeball N VI) and facial paralysis (N VII) on the side of the lesion, and hemiplegia on the other side In pontine affections, especially hemorrhage, a miotic pupil is common Lesions of the medulla are characterized by the "inferior type of alternating hemiplegia" in which the nucleus ambiguus (N IX and X), sometimes the spinal accessory nucleus (N XI) and frequently the nucleus of the hypoglossal nerve (N XII), or the corresponding nerves, are impaired on the side of the lesion Both medullary and pontine lesions are apt to be accompanied by signs of sympathetic disturbance, namely, a Horner's syndrome

The Basal Ganglia Accurate knowledge of the anatomy of the basal ganglia, more particularly of their neighboring and distant connections, is lacking Highly speculative concepts of disordered motility and tonus have been built on obscure anatomico-physiologic facts Moreover, there is considerable want of precision in the clinical use of the terms "basal ganglia" and "extrapyramidal system" Wechsler states "The terms 'irritative' or 'destructive' 'release,' and 'inhibition' are loosely used in the attempt to explain what cannot be understood Another source of confusion, if not of error is the indiscriminate correlation, in one breath, as it were of anatomical facts physiologic concepts, pathologic processes and clinical syndromes as if our present knowledge were sufficiently accurate to warrant such definite correlation"

Disorders of the Basal Ganglia In general it may be said that disease of the corpus striatum or striatal system is characterized by the following signs and symptoms, some of which are positive and some negative

(1) Rigidity that is general increase of muscle tonus

(2) Abnormal involuntary movements, e g , tremor, choreic movements athetosis and dystonia

(3) Poverty of voluntary, especially spontaneous, movements (hypo-

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an organic lesion, is dependent upon the part of the brain involved A motor aura consists of certain clonic twitchings of an extremity or part If, on the other hand, the aura is a disagreeable taste or smell, the lesion may be situated in the uncinate gyrus and the convulsion is known as an uncinate fit Likewise an aura may consist of visual hallucinations, such as flashes of light, or moving men or animals, in the former instance the lesion is in the occipital lobe whereas in the case of formed images a lesion of the temporal lobe is most likely

Electroencephalography Electrical discharges from the brain can be detected and graphically recorded by means of special instruments, just as the electrical discharges of the heart are recorded in the electrocardiogram The most characteristic feature of the normal electroencephalogram (E E G) of conscious persons is the "alpha rhythm," consisting of regular discharges of a frequency between 8 and 13 per second In sleep there appear certain slow, random waves termed 'delta waves The chief sign of cortical abnormality is the appearance of similar slow delta waves, the presence of discharges at a frequency of less than 7 per second in a waking adult may be taken as definitely indicative of disease (Walter) In children the normal limit is lower The mechanism of production of the delta waves is not known

Electroencephalography has proved of outstanding clinical value to the surgeon in the diagnosis and localization of cerebral tumors Walter has shown that the great majority of tumors which affect the cortex either directly by infiltration, or indirectly, produce in the nearby cortex a condition which causes a delta discharge to occur the new growth itself is entirely inactive electrically By means of records taken with three or more sets of leads a focus of delta waves can be localized, indicating the situation of the tumor A normal E E G is not conclusive evidence that no tumor is present, for in about 3 per cent of cases of cerebral tumor no abnormality is found in the electroencephalogram These have been cases of small meningioma or astrocytoma Cerebral abscesses may be located in the same way as cerebral tumors In many cases of idiopathic epilepsy cortical foci of delta waves are found, most often in cases of *grand mal* in the region of the superior frontal gyrus Walter states that excision of the delta focus in epileptic patients has resulted in only temporary clinical improvement (a *few months*)

In a case of intracranial aneurysm reported by Yeager and Walsh, ligation of the carotid arteries caused changes in the electroencephalogram principally a reduction in the frequency of the alpha rhythm However there was a return nearly to normal within a few days, this

kinesia) This is also a symptom of cortical, especially frontal, lesions

(4) Impairment of automatic associated movements

(5) Absence of "true" paralysis, that is, absence of signs of involvement of the pyramidal tracts

(6) Absence of sensory disturbances

Among the *syndromes* ascribed to lesions of the basal ganglia are paralysis agitans, progressive lenticular degeneration (Wilson's disease), pseudosclerosis of Westphal, dystonia musculorum deformans, striatal "pseudobulbar" palsies and Huntington's chorea The corpus striatum apparently has an inhibitory influence on lower segmental reflex activity Since tonus is the expression of a lower proprioceptive reflex, and the corpus striatum inhibits tonus, disease of this organ gives rise to increase of tonus and rigidity Kubit has advanced an explanation of abnormal movements on the basis of excitation waves traveling in closed circuits in the brain, similar to the circus movement in the heart muscle in certain cardiac arrythmias

Focal signs of disease of the brain are generally divided into irritative (positive) and paralytic (negative) It is not clear how an unchanging lesion can continue for years to cause irritative phenomena or how destructive lesions can give rise to spontaneous motor discharges To explain the latter the notion of "release phenomena" is invoked, by this is meant the unhampered discharge of motor impulses by a lower center when a higher inhibiting control is removed or destroyed

Abnormal Associated Movements · In every case of hemiplegia one may observe abnormal associated movements Some of them probably belong to the group of tonic neck reflexes, which are phenomena seen in decerebrate rigidity That tonus is a low proprioceptive reflex can be proved by cutting the afferent sensory fibers which convey the peripheral stimuli This is made use of in the Foerster operation for spasticity

Grasping and Groping Reflexes Grasping and groping reflexes, elicited by stroking the palms and the fingers, are significant of frontal lobe lesions They are also a characteristic feature of nicotinic acid deficiency encephalopathy of chronic alcoholic addicts, a syndrome described by Jolliffe, *et al*

Epilepsy By the general term "epilepsy" is understood a sudden either brief or prolonged loss of consciousness which is usually accompanied by a convulsion and followed by a period of more or less complete amnesia A number of other manifestations frequently precede, accompany or follow the epileptic attack

The aura that is the first symptom of an epileptic attack caused by

their destination As the axon fibers grow peripherally they exhibit no selectivity with regard to their pathway, that is, a motor fiber may grow in the sheath of a sensory nerve and vice versa Nerve fibers which have no neurilemma do not regenerate, that is the reason that regeneration does not occur within the brain and spinal cord

Within the central nervous system functional repair depends solely on the development of new paths for transmission of the lost functions, instead of repairs of the old paths The time required for regeneration is not well known, but it varies with the length of degenerated fiber and may be a few or many months Sensation is recovered much more rapidly after crushing of a sensory nerve than after its division by cutting The prospect of success of surgical repair of a divided nerve is closely related to the interval which elapses between the time of injury and the time at which suture is performed

Effect of Alcohol Injection Ruth and others state that the pathologic change found in sensory nerves and their ganglion cells after injection of from 80 to 95 per cent alcohol is a Wallerian degeneration the same as though the nerve had been cut Thirty three and one third per cent alcohol has been used clinically by Labat without causing muscular paresis or paralysis

CLINICAL FEATURES IN PERIPHERAL NERVE INJURIES

The prominent clinical manifestations of peripheral nerve injuries are disturbances of

1 Motility
2 Sensation
3 Vasomotor Control
4 Spinal Reflexes
5 The Reaction of Degeneration

Motor Changes Following Nerve Injury Following *contusion* of a nerve as by a gunshot wound of the adjacent tissues there may be a brief period of motor paralysis, probably due to transient pressure and edema There is rarely any loss of sensation associated with the condition

Electrical Tests for Motor Nerve Lesions Electrical testing of motor function has value only in the lower motor neuron type of paralysis and in muscle atrophy, that is in anterior horn disease, peripheral nerve lesions and the myopathies The *reaction of degeneration* consists of certain alterations in the responsiveness of muscle and nerve to electrical stimuli following severance of a motor nerve The nerve within three or four weeks becomes completely inexcitable by either interrupted

Changes in the Nerve Fiber: *The proximal* portion of the divided nerve fiber ordinarily degenerates upward for only a short distance, not more than about 2 centimeters This retrograde degeneration is only temporary but sometimes it proceeds much farther and may ascend even to the cell body within the spinal cord so that the entire neuron atrophies and disappears Myelinated fibers may undergo no central degeneration at all, but instead start to grow immediately after the injury Unmyelinated fibers begin to regenerate about the 14th day

Distal to the point at which it is severed, the nerve fiber begins to degenerate within 24 hours, and by the third day it has lost the power of conducting nerve impulses Conductivity is not lost immediately, normal electrical reactions being present during the first few days despite the total muscular paralysis If after two weeks following a nerve injury faradic stimulation still induces contraction, it indicates that the nerve fibers are not severed and recovery will be completed rapidly, that is, within three to six weeks It is said that when the cut ends of a severed motor nerve are promptly approximated neatly under local anaesthesia in man, voluntary movements may be performed immediately and for a number of hours thereafter by reason of volitional nerve impulses which are conducted across the gap at the point of contact of the severed ends In the dog, the degenerative changes occur simultaneously along the whole length of the severed peripheral portion of the nerve fiber and proceed rapidly, in the rabbit and in man, the degeneration extends slowly toward the periphery and is complete within three or four weeks

At the site of the lesion there is a temporary attempt at repair for a distance of about 1 mm at the cut end of both the proximal and distal segment, in that these form a localized branching reticulum of nerve filaments This disappears in about three weeks The axis-cylinder splits into lengths The myelin sheath breaks up to form fat droplets of various sizes The surrounding neurilemma thickens and its cells multiply and, as the remains of the axis cylinder and myelin sheath are removed by phagocytes from the neighborhood, the neurilemma fills their place with a solid mass of granular cytoplasm containing many nuclei This cellular tube or column gives guidance and perhaps also nutrition to the regenerating fiber Complete regeneration of the nerve fiber may then follow, if close and accurate contact of the divided ends is accomplished, by means of bundles of neurofibrils from the stump of the nerve fiber extending into and also between the cytoplasm-filled tubes representing the remains of the peripheral portion of the nerve Many of these fibrils become lost but many succeed in growing out to

with slow contraction The muscles which cooperate to produce a given movement have the same chronaxies The chronaxie of a nerve is the same as that of the muscle which it innervates, this is called the law of isochronism The chronaxie of a muscle or nerve changes significantly as a result of trauma and degeneration In the case of degeneration the change in chronaxie varies with the degree of the lesion, that is, the number of fibers involved

Practical applications of chronaxie in surgery are pointed out by Osawa and Nagai These observers find chronaxie determinations of assistance in making a localizing diagnosis of spinal cord and peripheral nerve lesions

Often the earliest indication of the recovery of voluntary motion is the ability of the patient to maintain for a short time a position induced by electrical stimulation of the muscles, at a time when he is unable to maintain the same position if it is produced passively Electrical testing may be of help in the diagnosis of severed or adherent tendons, in the presence of which stimulation with the interrupted current induces muscular contraction but no corresponding motion of the limb

Motor Disturbances of the Hand Following Nerve Injury Typical median nerve or ulnar nerve deformities of the hand cannot be described without reference to the level at which the lesion is situated, that is, whether it is above the branches of the muscles of the forearm or is near the wrist, the innervation of the forearm muscles remaining intact

Paralysis of the Lumbrical Muscles Median and ulnar nerve lesions at the wrist produce, among other signs, characteristic attitudes of the fingers depending on loss of function of the lumbrical muscles In the case of the median nerve only the index and middle finger are thus affected, and in the case of the ulnar nerve only the ring finger and little finger The chief action of the lumbrical muscle is to flex the proximal phalanx of the digit its function however is not to produce actual motion, for it is a very weak muscle, but to steady the proximal phalanx and keep it straight, in order that the long flexor and extensor muscles may act upon the distal phalanges in a suitable manner The extensor tendon, for example, passes over the several joints of the digit to be inserted into the distal phalanx When acting by itself alone, it is apparent that, though it could cause only extension if there were only one joint free to move, the presence of several joints permits the part to "buckle," and the net effect is shortening of the digit as a whole, with extension at one part (proximal phalanx) but flexion at the other part (distal phalanges) The lumbrical muscle merely prevents the

(faradic) or constant (galvanic) electrical currents In every instance the nerve is tested with the interrupted current first If there is a normal response, there is no need of testing with the constant current The muscle changes are described as quantitative, qualitative, modal and polar in nature All of these with the exception of the modal changes refer to stimulation by means of a constant current

1 Modal When stimulated by an interrupted (faradic) current, the muscle exhibits progressive loss of responsiveness, and in about two weeks becomes completely inexcitable to this mode of stimulation

2 Quantitative With constant (galvanic) current the muscle continues to respond but is hyperexcitable at first, later hypoexcitable, and becomes completely inexcitable in from 12 to 24 months

3 Qualitative Contractions elicited by the constant current are sluggish This slowness of the muscular contraction is the only constant phenomenon satisfactory for the determination of the reaction of degeneration

4 Polar Normally, the response to stimulation with the cathode applied over the nerve and muscle is greater than that to stimulation with the anode (CCC > ACC) In the reaction of degeneration, so-called polar inversion occurs, that is, anode stimulation is greater than cathode stimulation (ACC > CCC) This sign is inconstant and unreliable It may occur in normal muscles, as for instance, when a muscle has been chilled

In local muscle disorders and in the myopathies, the electrical changes are only quantitative in nature, not qualitative, the latter occur only in cases of involvement of the lower motor neuron Electrical examination by itself does not give absolute proof of degeneration of a motor nerve, at least it does not indicate inability to recover spontaneously Even when a complete reaction of degeneration is obtained, it alone is not sufficient indication of an irreparable lesion within the first year after the injury It is true, however, that after one or at most two years, an irreparable lesion is always associated with complete loss of response to all electrical stimuli

In the initial phase of the electrical changes, that is, for a period of about 10 to 14 days, there is progressive diminution in the response to stimulation of the muscle with interrupted current, whereas the response to constant current is at first increased but gradually becomes more and more sluggish

Chronaxie Changes in Nerve Lesions There is a close relation between the *chronaxie* and the speed of contraction of a muscle, in general, short chronaxie is associated with quick contraction, long chronaxie

nerve injuries Appreciation of sharpness of an object is not synonymous with the sensation of pain and should not be confused with the latter

Sensory Overlap The terms "protopathic" and "epicritic" refer merely to coarse and delicate cutaneous sensations, respectively The distinction between them is of some use clinically, though the original explanation on the basis of more rapid regeneration of one group of nerve fibres (protopathic) has been discarded The coarse (protopathic) sensations (pain and extremes of temperature) return earlier following a nerve lesion because there is more overlap from adjacent nerves for these qualities than for the more delicate (epicritic) sensations (milder temperatures, light touch and tactile discrimination) That is, "protopathic" nerve endings of neighboring uninvolved nerves are present in a large part of the area of distribution of the affected nerve An enormous overlap for these coarser sensations "develops" or rather becomes manifest within a few weeks or months and is early misinterpreted as early "recovery" on the part of the injured nerve itself It is not clear why the sensory function of these overlapping healthy fibres is not active immediately after the nerve injury Except for this rather short latent period, it may be said that there is only partial anesthesia for the coarser sensations from the beginning Delicate grades of sensation, on the contrary, are really lost completely in the greater part of the area of distribution of the affected nerve, for there is little overlapping of these types of fibres This is the reason for the apparent longer recovery period of the epicritic qualities of sensation

After lesions of single cutaneous nerves, the area of total anesthesia usually shrinks rapidly because of sensibility derived from neighboring nerves as just described Sometimes in fact there is only partial anesthesia from the beginning that is no region of total anesthesia results the overlapping is so complete Another element of sensation which may be retained is deep sensibility of muscles and tendons, which is conveyed by fibres in the uninvolved motor nerves

Area of Exclusive Sensory Supply The early return of pain sensibility, as to a pin-prick, which may occur within from 30 to 100 days is not evidence of incomplete severance of the nerve or of beginning regeneration if the region tested lies within the *area of possible overlap* from adjacent nerves For positive evidence of regeneration it is necessary to test the area known to be supplied *exclusively* by the injured nerve This area varies in different individuals and is always very small in comparison with the total area of distribution of the nerve For example the only region of the hand supplied exclusively by the median

'buckling' by preventing the extension of the proximal phalanx, the extensor tendon is thereby enabled to cause extension of the distal part of the finger

Median Nerve Severance at the Wrist If a patient with a severance of the median nerve at the wrist attempts to hold all the fingers straight the index and middle finger will be seen to be displaced backward a little, that is, to be in a plane a little behind that of the fourth and fifth fingers in addition, the index and middle fingers are slightly curved or hooked, that is flexed a little at the interphalangeal joints This appearance of the digits is attributable to loss of the flexing action of the lumbrical muscle upon the proximal phalanx If, while the patient is trying ineffectually to hold the fingers straight, the examiner supplies the missing lumbrical action by flexing the proximal phalanx until it is straight in line with the hand, the hooked attitude of the finger disappears, the distal phalanges straightening out automatically The curved state of the index finger in such a median nerve lesion (if exaggerated) resembles the attitude which this digit assumes in pulling the trigger of a gun, hence it may be termed "trigger index" The middle finger exhibits the same deformity

Ulnar Nerve Severance at the Wrist In a lesion of the ulnar nerve at the wrist, the curvature and backward displacement of the digits described above as characteristic of lumbrical paralysis are found, but in this case they are present only in the fourth and fifth fingers, the others being straight The attitude of the little finger in such an ulnar lesion (if exaggerated) resembles the position in which some persons hold this digit when holding a teacup, hence it may be termed "teacup pinky" The ring finger exhibits the same deformity

Sensory Changes Following Nerve Injury · Sensory nerve lesions often cause a peculiar unpleasant hyperesthesia somewhat like a diffuse sense of pain in the affected area This effect is noted chiefly in incomplete nerve severance and in recovering lesions Causalgia reaches its acme in about four or five months after the nerve injury It has been observed in the right hand following injury of the left median nerve In examining for sensory changes fatigue readily occurs, especially when some impairment of sensation is present Therefore it is necessary to avoid errors due to rapid repetition of tests in a given area In testing the sense of light touch indentation of the skin must be avoided, cotton being used as the stimulus Tactile discrimination, that is, the ability to recognize as discrete two stimuli applied to two points on the skin simultaneously ("two-dimensional localization"), though of significance in spinal cord lesions, affords no valuable clinical data in peripheral

normally by reason of immobilization of the limb Sweating is absent if the nerve lesion is complete, if the lesion is partial, hyperidrosis is common, usually accompanied by some pain

Diagnosis of Nerve Injuries The diagnosis of a complete nerve lesion is usually simple, though it is often impossible to distinguish contusion and compression from actual severance until some months have elapsed A single examination only shows whether the lesion is complete or incomplete, if it is complete, absence of actual division of the nerve can be determined only by the subsequent return of function that is, by the clinical course *There is no way to decide the matter early*, or to determine early whether operation is needed In a partial nerve lesion there may be little or no sensory loss, and the reaction of degeneration is often of great service in discovering the lesion If the reaction of degeneration is obtained, a nerve lesion is present.

The degree of atrophy and the rapidity with which it takes place are not decisive as to whether a lesion is reparable For example, there is generally extensive atrophy in ulnar nerve lesions, regardless of their severity No help in prognosis is derived from trophic changes, changes in muscle tone, tenderness of the muscles or nerve trunk or hyperaesthesia. Testing of the motor reflexes is usually not an important aid in the clinical management of peripheral nerve injuries

Sensory Signs of Nerve Regeneration Tinel's sign is a tingling or other type of paraesthesia occurring in the part supplied by the nerve on percussion at first over the site of injury and later at progressively greater distances distal to the site of injury It first appears at the site of injury after from three to six weeks, and moves distally at about 1 to 2 millimeters per day One month after its appearance it has moved about 2 centimeters, after two months 5 centimeters and after three months 9 5 centimeters distal to the site of the lesion, the rate of progression varying in different cases After about 100 days the sign disappears In testing for Tinel's sign, percussion should be begun peripherally Tinel's sign is valueless as an indication of regeneration as long as it is found only at the site of injury, when it is probably dependent on neuroma formation It is of little value generally, inasmuch as it may be absent in over 10 per cent of recovering cases

Pollock and Davis have found that frequently a spontaneous ache and a vague "different feeling" in the affected part are the earliest signs of recovery of *sensibility* these signs do not necessarily indicate *regeneration* of the injured nerve, but are referable to overlap of sensory nerves Then so-called protopathic sensation returns, followed by epicritic sensation but these too develop from the overlapping nerves,

nerve is the tips of the second and third digits In the hand the radial nerve supplies exclusively only the dorsal aspect of the roots of the first and second digits, and in some cases there is no strictly radial area whatever, because of more extensive overlapping than usual

Dissociated Early Return of Pain Sense That the process of nerve regeneration does not restore pain sensibility earlier than tactile sensibility can be shown experimentally When pain sense has returned in a given region without touch sense, it is found that dividing the supposedly regenerating injured nerve does not cause analgesia to recur in the area in which pain sensibility had returned Therefore this return could not have been due to partial regeneration of the nerve Such dissociated return of pain sense is found nowhere except in an area of overlap, and is mediated by neighboring nerves

Vasomotor, Trophic and Secretory Changes Following Nerve Injury The exact relation between peripheral nerve injuries and trophic, vasomotor and secretory disturbances is not entirely clear These disturbances may be due in part at least to coincident injury to blood vessels, or due to immobilization of the part They are much less marked in complete interruption of a nerve by trauma than in partial lesions Whenever the skin is insensitive to pain it is particularly liable to injury and ulceration, and relatively slight increases in temperature cause blistering Sometimes blood blisters arise spontaneously Irritants applied to an anaesthetic area do not induce hyperemia and swelling as in normal skin Yet healing of a wound proceeds as in normal tissues, providing repeated injury is not inflicted Trophic changes are dependent mainly if not entirely upon affections of the sensory cerebrospinal nerves The latter convey nearly all the vasodilator impulses whereas vasoconstrictor nerve fibers belong exclusively to the sympathetic system The loss of the normal reactive, i e, protective hyperemia in response to surface stimuli is probably the chief factor in the production of neurotrophic sores

Rarely after a peripheral nerve injury the anaesthetic skin becomes glossy Frequently desquamation fails to proceed normally, the skin becoming dry, rough, scaly and inelastic Hypertrichosis is common but is probably due to factors other than the nerve lesion itself, for it is not confined to the distribution of the affected nerve After section of the sensory root of the trigeminal (fifth cranial) nerve, no difference in the growth of hair on the face has been noted After removal of the inferior cervical and first thoracic sympathetic ganglia, which supply the skin of the face, the hair tends to grow more strongly on the side operated on After a nerve injury, the nails grow at a slower rate than

it, (2) to mediate nutrient exchanges of the nervous tissue, and, possibly, (3) to convey hormones

CIRCULATION OF THE CEREBROSPINAL FLUID

The cerebrospinal fluid is produced by the choroid plexus in all the five ventricles of the brain, and passes into the cisterna magna, whence it is distributed throughout the subarachnoid space over the surface of the brain and spinal cord It is believed to be formed largely by a process of filtration but it cannot be a mere transudate because it contains more crystalloids than the blood serum, there is probably an active secretory process also That there is some selective action is indicated by the fact that practically no bile appears in the spinal fluid even in cases of deep jaundice Bile pigments may be formed from blood in the subarachnoid space by the action of "meningocytes" Diffusion from the subarachnoid space into the subdural space does not occur Under abnormal conditions (e g, trauma) as much as 1000 cubic centimeters of spinal fluid per day may be drained off by lumbar puncture, the amount normally produced in a day is unknown but is much less than this Volatile anaesthetics, especially ether, considerably increase the formation of spinal fluid Absorption of the cerebrospinal fluid occurs chiefly in the supratentorial region, where the fluid is taken up by the cerebral veins and probably also by the arachnoid villi and the capillaries of the pia arachnoid Absorption by the spinal veins also occur

Hydrocephalus Interference with the escape of cerebrospinal fluid from any or all of the ventricles leads to internal hydrocephalus Internal hydrocephalus is frequently congenital, the pathogenesis of the condition is unknown in many cases hence it is termed primary or idiopathic Acquired internal hydrocephalus results when any interference with the outflow of fluid from the ventricles is produced by trauma or disease, tumors of the posterior fossa and meningitis are the most common causes External hydrocephalus is the presence of excess fluid outside the brain By itself it is comparatively rare, occurring chiefly in association with congenital anomalies Combined internal and external hydrocephalus, which can result from impaired absorption of the cerebrospinal fluid into the circulation is more common Increased pressure in the sheath like projection of the subarachnoid space surrounding the optic nerve impedes the blood flow in the veins of the nerve more than in the arteries the veins become swollen and fluid exudes from them causing papilledema Frequently it takes 14 days

that is, there is only a "shrinkage" of the anesthetic area Reports of the successive sensory changes following nerve lesions vary greatly, and the lack of consistency in the findings is chiefly due to lack of uniformity in the technique used to determine the sensory status

Motor Signs of Nerve Regeneration Disappearance of muscle atrophy and recovery of muscle tone are not of much value as clinical signs of regeneration because they are so variable The degree of tone present closely parallels the amount of motion to which the part is subjected, and in any case cannot readily be measured with accuracy The disappearance of the reaction of regeneration is of some value, the most reliable sign being an increased rapidity of contraction in response to stimulation with the constant (galvanic) current The return of excitability with interrupted (faradic) current never precedes the return of voluntary contraction in complete lesions, it sometimes does in partial lesions Voluntary contraction of the involved muscles is definite evidence of recovery, but must be carefully distinguished from movement effected by the supplementary function of neighboring muscles, a distinction which is often difficult to make

Order of Appearance of Reliable Signs of Regeneration Pollock and Davis found that the order in which the most reliable signs of recovery of a nerve appear is as follows

1 Sensibility to pain, e g , pinch, in the area of *isolated* supply of the nerve
2 Spontaneous aching in the involved muscles
3 Voluntary motion
4 Sensibility to other types of stimuli
5 Excitability of the muscles with interrupted current

The earliest time of beginning spontaneous recovery of sensory and motor function without operation, is commonly about 5 months after the injury *In some cases, however, it is as much as 18 or even 24* months after the injury In cases of primary nerve suture, beginning recovery is generally first detectable after about eight or nine months Any functional recovery detected within a few months after the injury cannot be interpreted as evidence of regeneration of the severed nerve, however gratifying in itself the improvement may be

THE CEREBROSPINAL FLUID

FUNCTIONS OF THE CEREBROSPINAL FLUID

The functions of the cerebrospinal fluid are (1) to serve as a mechanical protection for the central nervous system, which floats within

determined Continued loss of fluid through the puncture hole has been suggested Excessive secretion because of the irritation, or perhaps in over-compensation for the amount of fluid lost, would seem to be a more plausible explanation Lumbar puncture often relieves headache due to increased intracranial pressure Headache from this cause is aggravated by sneezing or coughing Sudden reduction of intracranial pressure may itself induce severe headache It is likely that the afferent pain fibres for such headaches arise in the blood vessels of the pia, for the dura and the brain substance are insensitive

Forced Drainage of Cerebrospinal Fluid Kubie and Retan have proposed forced drainage of cerebrospinal fluid in meningitis for the purpose of mobilizing any inflammatory exudate and carrying it from the depths of the central nervous system to the surface and out through the drainage needle They believe that since normal cerebrospinal fluid pressure is greater than atmospheric pressure it ordinarily tends to inhibit transudation of fluid from the arterial end of the capillaries and to accelerate reabsorption at the venous end When lumbar puncture is performed and the fluid is allowed to drain freely, intracranial pressure is reduced to atmospheric pressure and thereby the physical conditions of fluid protection are made to conform to those which obtain throughout the rest of the body The production of free cerebrospinal fluid can then be increased by lowering the osmotic pressure of the blood stream by dilution

Forced drainage consists then of two steps first, the reduction of intracranial pressure to atmospheric pressure by spinal or cisternal puncture in order to make the intracranial conditions of fluid production conform to those in the rest of the body, so that all the capillary bed takes part in fluid formation, second dilution of the blood by the intravenous injection of hypotonic saline solutions Under these conditions the formation of cerebrospinal fluid takes place not only by secretion at the choroid plexus but also by transudation from the capillaries throughout the parenchyma of the brain and spinal cord No diffuse swelling or hydration of the nervous system occurs little or no increase in intracranial pressure takes place and the fluid formed courses along the perivascular channels until it reaches the subarachnoid space There is some evidence that the procedure may increase the transfer of immune bodies from the blood to the cerebrospinal fluid In the course of one to three hours one gives 1 to 3 liters of hypotonic salt solution, the concentration varying from 0 45 per cent downward, depending on the fragility of the red cells of the individual patient and the rate at which the fluid is to be given

or more of increased intracranial pressure for this to develop It is generally bilateral, only rarely unilateral The most common cause of papilledema is tumor of the brain Among other causes are brain abscess, hydrocephalus, subarachnoid hemorrhage, fracture of the skull and sinus thrombosis

PRESSURE OF THE CEREBROSPINAL FLUID

Mechanical Factors in Cerebrospinal Pressure. The pressure of the cerebrospinal fluid is normally 100 to 150 millimeters of water in the recumbent position, and 200 to 250 millimeters in the sitting position The cerebrospinal fluid does not mix with the lymph to any appreciable extent, even in the perivascular lymphatics The pressure present during life is circulatory in origin, for in the cadaver the pressure of the cerebrospinal fluid is zero Coughing and straining raise the pressure several centimeters When the subarachnoid space is free of obstruction, the pressure is the same throughout its extent Blockage results in marked increase of pressure above the block and normal or subnormal pressure below it

The cerebrospinal fluid pressure varies with the venous pressure but must be higher than the latter since the cerebrospinal fluid flows into the cerebral veins Cerebrospinal fluid pressure must be lower than capillary pressure, otherwise the brain capillaries would be compressed and the blood supply of the brain would be shut off In view of the pressure relations, intracranial hemorrhage from capillaries could in some instances be more serious than hemorrhage from the much larger veins In fact, it is difficult to understand how any considerable hemorrhage of purely venous origin can occur within the cranium, however large the injured vein, since the surrounding intracranial pressure, equal to the cerebrospinal fluid pressure, is greater than the venous pressure and tends to prevent escape of blood from the veins

In surgery, diagnostic lumbar or cisternal puncture is performed most frequently to determine the pressure relations of the spinal fluid and the presence or absence of gross or microscopic blood or of xanthochromia Hemorrhage dating back a week or more may produce xanthocromia, but the latter is not pathognomic of hemorrhage, for it may occur also below the level of subarachnoid block from any cause

Cerebrospinal fluid may be withdrawn for the purpose of reducing intracranial tension by either spinal, cisternal or ventricular puncture It is frequently withdrawn for the induction of spinal anesthesia The cause of the headache which sometimes occurs following lumbar puncture, even when only a small amount of fluid is removed, has not been

lin ratio is the same as in the blood and fibrogen is present so that the fluid coagulates spontaneously The white cell count remains normal Xanthochromia, increased protein content and spontaneous coagulation, with no increase in cells constitute the "loculation syndrome" of Froin which signifies spinal blockage The increase in the protein content is the only essential feature of the syndrome, as xanthochromia and spontaneous coagulation may be absent Occasionally xanthochromia and even coagulation may occur above as well as below the level of block in cases of tumor of the cauda equina in these instances however the protein content is less above the lesion than below The rapid onset of paraplegia following lumbar puncture is practically diagnostic of tumor of the spinal cord, which is a common cause of spinal block The majority of spinal cord tumors are extramedullary and intradural

When lipiodol which is a nontoxic fluid heavier than spinal fluid and opaque to x rays, is injected into the cisterna magna with the patient in the upright position, it falls to the point of blockage and indicates the level of the latter on the x ray film It requires months or years for the lipiodol to be absorbed In approximately two-thirds of the patients re-examined by x ray one to 14 years after lumbar myelography with lipiodol, Garland and Morrissey found intracranial collections of the iodized oil No neurological symptoms or signs could be ascribed to the presence of the oil

Tests for Spinal Block There are two commonly used manometric methods for determining the presence of block namely direct pressure measurements by simultaneous cisternal and spinal punctures, and spinal puncture with digital compression of both jugular veins (Queckenstedt method) In the latter method the jugular compression is normally followed by a sharp rise in pressure to 350 or 500 millimeters of water and a sharp fall The rise occurs within from 10 to 12 seconds and the fall does not take more than 15 seconds If there is a partial block there is only a slight rise which takes place slowly and is followed by a slow fall, the rise requiring about 20 seconds and the fall to the initial level more than 25 seconds If there is a complete block, no rise in pressure occurs on jugular compression In the presence of blockage coughing and straining still cause an increase of pressure Sometimes combined cisternal and lumbar punctures are used in the Queckenstedt test to determine whether the block is between these two levels or is above the cisterna magna Rise of pressure on compressing the jugular vein on one side with no rise when the vein of the opposite side is compressed signifies sinus or jugular thrombosis on the side on which no rise occurs Meredith states that the Queckenstedt test should

Intracranial Tumor An increase in intracranial pressure due to a tumor usually is not distributed throughout all portions of the cranial cavity The falx cerebri and falx cerebelli check the spread of the pressure to some extent, and may prevent early effects upon the vital medullary centers Similarly, cerebellar tumors may not cause disturbances of consciousness until a late stage It is desirable, therefore, that decompression operations be performed as near the site of the tumor as possible

Radiculitis In radiculitis, sneezing, coughing or straining often intensify the pain if the nerve roots are affected intervertebrally, because of the change in pressure in the cerebrospinal fluid In many cases of spinal cord tumor, the patient will experience pain at the level of the tumor during the Queckenstedt test even when straining or coughing had never previously produced pain

Herniation of the Brain It has been generally held that herniation of the cerebellum into the foramen magnum producing pressure paralysis of the medullary cardiorespiratory centers is a common immediate cause of death in cases of intracranial compression In chronic slowly developing states of increased intracranial pressure marked cerebellar herniation may gradually occur without producing acute medullary compression symptoms, but showing itself clinically as a midline cerebellar syndrome According to Schaller there is no proof of sudden wedging or movement of the contents of the posterior fossa following spinal tap even in the presence of increased intracranial pressure He believes that the so-called herniation may be in reality general swelling and edema of the brain, the latter being produced by sudden and excessive withdrawal of fluid The incidence of postpuncture accidents is greater in supratentorial than infratentorial tumors Fatalities after ventriculography are usually due to effects of the procedure upon the pressure conditions within the cranial cavity Encephalography is more dangerous and causes a more severe general reaction than ventriculography particularly in cases of increased intracranial pressure It is absolutely contraindicated in any case in which a posterior fossa tumor is suspected or in which the intraspinal pressure exceeds 200 millimeters of water

Spinal Block Spinal blockage, e g , by cord tumor, obstructs the spinal veins in which the flow is normally upward, so that below the level of the block serum proteins and red blood cells exude into the spinal fluid The blood pigment becomes altered so as to give the spinal fluid a yellow color (xanthochromia) The protein content rises to 0 5 per cent or higher, and may even reach 4 per cent The albumin globu-

mercury during the first 30 minutes, then a gradual rise to a point above the initial pressure in two hours This increase amounted in some cases to as much as 50 per cent of the original pressure The initial pressure was restored in 24 hours In other cases there was an immediate and steady rise with slight fluctuations for two hours followed by a gradual fall to the initial pressure in 24 hours In about half of all cases the blood pressure rose and the respiration became labored, these effects being more marked with the 50 per cent solution than with the 25 per cent solution Headache was relieved for a short time in some cases, but not to the degree of relief obtained by lumbar puncture. These results seem to indicate that hypertonic dextrose solutions not only do not appreciably lower intracranial pressure as measured directly by the spinal manometer, but in many cases actually increase the pressure Masserman obtained similar results in experiments on normal individuals

Hypertonic Sucrose Solutions Hahn, *et al*, found sucrose solution (50 per cent) to have considerable advantage over dextrose solutions in the osmotic therapy of increased intracranial pressure occurring in cases of acute brain injury The advantage is due to the fact that sucrose cannot diffuse across cell membranes

In the normal unanesthetized dog, and also in patients with severe head injuries, Webster and Freeman found that intravenous hypertonic solutions of glucose and of sucrose had the same effects, namely a temporary fall of cerebrospinal fluid pressure They observed no secondary rise to a level above the normal pressure Isotonic fluids given intravenously caused a moderate increase in the cerebrospinal fluid pressure

Lypophile Serum Hughes, *et al*, have given human lypophile serum (concentrated pooled human serum) dissolved in water intravenously for the reduction of increased intracranial pressure They found it highly effective the reduction in pressure persisting for relatively long periods

Osmotic Factor in Subdural Hematoma The late onset of symptoms of increased intracranial pressure in subdural hematoma, which was for a long time unexplained, has been shown by Gardner and by Zollinger and Gross to be due to osmotic pressure changes within the hematoma The blood in the central part of the hematoma gradually undergoes disorganization, the larger molecules becoming broken up into smaller ones so that the total number of molecules is increased As a result the osmotic pressure in the interior of the extravasated

not yet be performed routinely on all patients subjected to encephalography or even lumbar puncture, as in most cases it yields little or no pertinent information and may do irreparable harm

In a certain percentage of cases there are normal dynamics before cerebrospinal fluid is removed, but partial or complete block becomes manifest after from 5 to 10 cubic centimeters has been removed The removal of the fluid decreases the intraspinal pressure sufficiently to permit the dura and arachnoid to come in contact with the edges of the tumor and cord, thus producing the block Inhalation of amyl nitrite normally induces a prompt rise and fall of pressure in the cerebrospinal fluid When there is a complete block, the rise fails to occur below the level of the block, in partial block there is a slow rise and a slow fall of reduced magnitude According to Elsberg and Hare the amyl nitrate manometric test is a delicate method for determining the presence or absence of block and the degree of interference with the free flow of cerebrospinal fluid, and is perhaps more sensitive than the manometric tests with jugular compression

Osmotic Factors in Cerebrospinal Pressure Hypertonic solution of sodium chloride or dextrose administered by vein, by duodenal tube or by rectum causes experimentally in the normal animal a fall of cerebrospinal pressure, which then returns to normal in 12 to 48 hours By raising the osmotic pressure of the blood, the direction of flow of the cerebrospinal fluid may even be reversed for a time This is of great temporary benefit in internal hydrocephalus Also in cases of brain tumor, headache and papilledema may be decreased for a few days by this means, operation is then safer and there is less bulging of the brain when the skull is opened However, patients treated in this manner sometimes develop convulsive attacks and labored breathing, and some lapse into coma and die The brain cells give up some of their fluid content for a brief period while the salt or dextrose is still in the blood stream, but later when the salt or dextrose has passed from the blood vessels into the brain cells, fluid flows back again into the cells and the swelling of the brain recurs to a greater extent than had existed before

Hypertonic Dextrose Solutions In order to determine accurately the efficiency of the intravenous dextrose method in acute cranial injury in man, Jackson, *et al*, used it in 20 cases in which manometric measurements of cerebrospinal fluid pressure were made in the lumbar region Solutions of 25 per cent and 50 per cent were used In some cases there was an initial drop in pressure of from 1 to 4 millimeters of

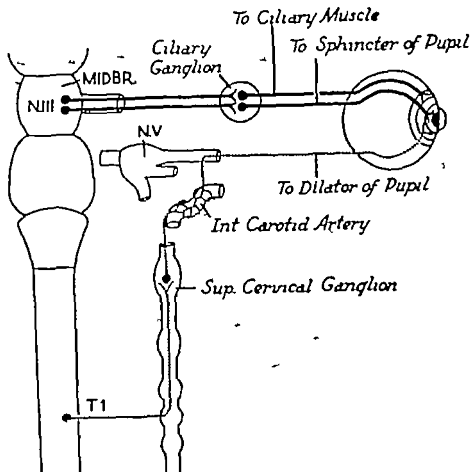


FIG 31 Autonomic innervation of the orbit. The ciliary ganglion. (From Gray's *Anatomy* 23rd Edition Courtesy of Lea & Febiger Publishers.)

fiber) and join a spinal nerve Every spinal nerve has a grey ramus Through the spinal nerves the postganglionic fibers are distributed to the blood vessels and sweat glands in the somatic realm Secondly, the postganglionic fibers may travel in the plexus about blood vessels to reach their effector organs This is especially true of the sympathetic supply to the head, abdominal and pelvic organs Thirdly, they may form independent pathways, as in the case of the cardiac sympathetic nerves

Sympathetic Innervation of the Head and Neck The fibers for the head and neck (derived from spinal segments T 1 and T 2) on reaching the sympathetic trunk pass upward, without interruption, to the superior cervical ganglion, and there terminate in synaptic relationship with the cell bodies of postganglionic fibers (A few synapses for the head region have been found in the stellate ganglion) The postganglionic fibers for the head and neck, therefore, arise in the superior cervical ganglion They are conveniently distributed to the periphery as follows

pointed out that the *sympathetic system when stimulated prepared* the animal for "flight" or "fight" Constriction of the vessels of the skin and viscera results, causing a shift of the blood to the organs necessary for struggle The vessels in skeletal muscle and in the heart become dilated The cardiac rate is accelerated, respirations are deepened, the pupils become dilated and sweating occurs These are typical manifestations of fear in an animal and to a considerable extent in the human Cannon considered the *parasympathetic system to be concerned* with protection, conservation and restoration of the bodily resources All processes essential for digestion and absorption of food, including excretion of the various digestive juices and peristalsis, are a result of parasympathetic activity

Furthermore, the two systems appear to be related to different chemical mediators Adrenalin or sympathin is the chemical substance formed at the sympathetic postganglionic terminal nerve endings, while acetylcholine is the substance liberated at the analogous nerve endings of the parasympathetic system

In all these respects the sympathetic or thoracolumbar division stands in contrast to the parasympathetic or craniosacral division

THE THORACOLUMBAR OUTFLOW (SYMPATHETIC)

Distribution of Preganglionic Fibers: The cells of origin of the preganglionic fibers of the sympathetic division are situated in the lateral horns in that portion of the spinal cord which is between the first thoracic and second lumbar segments inclusive Only the anterior roots arising from these segments of the spinal cord contain any preganglionic fibers as they emerge from the spinal cord These preganglionic fibers (myelinated fibers) leave the anterior root through the white ramus communicantes and go to the corresponding sympathetic ganglion Having reached the ganglion, the preganglionic axon may 1 End and synapse in its own ganglion 2 Ascend in the sympathetic trunk and synapse in a higher ganglion 3 Descend in the sympathetic trunk and synapse in a lower ganglion 4 Travel through the sympathetic trunk and leave still as a preganglionic fiber and travel with similar fibers in what are the splanchnic nerves There are three thoracic and two or three lumbar splanchnic nerves These preganglionic fibers then synapse in the prevertebral ganglia and are concerned with the innervation of the abdominal and pelvic organs

Distribution of Postganglionic Fibers Each preganglionic axon synapses with 10 to 20 postganglionic neurones The postganglionic fibers may leave the sympathetic trunk by a grey ramus (unmyelinated

ganglia, superior, middle and inferior, in each of which some of the fibers terminate. Corresponding postganglionic fibers start in each ganglion and form the upper, middle and lower sympathetic cardiac nerves, which pass from the respective cervical ganglia down through the neck and thorax by a course independent of blood vessels or somatic nerves They supply both the heart and the lungs, being distributed to these organs by the cardiac and pulmonary plexuses respectively Some sympathetic fibers pass directly to these plexuses from the upper thoracic segments without ascending to the cervical region

The sympathetic preganglionic fibers for the thoracic wall are quite short, inasmuch as they terminate in the thoracic sympathetic chain ganglion belonging to the segment in which they arise The postganglionic fibers begin in these chain ganglia and are distributed segmentally to the wall of the thorax by accompanying the corresponding intercostal nerves

Sympathetic Innervation of the Abdomen The preganglionic fibers for all the abdominal viscera situated above the pelvic cavity arise in the lower thoracic and upper lumbar segments of the spinal cord (T-4 to L-2) and form the three splanchnic nerves, by which they pass to the celiac ganglion and the other prevertebral ganglia which are continuous with it, such as the superior mesenteric, renal, etc These extensions of the celiac ganglion are situated about the origins of the arteries supplying the various organs Together with the celiac ganglion they may be considered to form a unit in which are located the synapses of the sympathetic supply to all the (extrapelvic) abdominal viscera the superior mesenteric ganglion being the chief site of these synapses The postganglionic fibers, starting in these ganglia, reach their destination by accompanying the blood vessels

The pelvic viscera are supplied with preganglionic fibers in an analogous manner by the lesser splanchnic nerve (T 10 to T 11), the lowest splanchnic nerve (T 12) and the upper lumbar nerves (L 1 and L 2) These upper lumbar visceral nerves pass to and through the sympathetic trunk without interruption, and may be looked upon as a continuation of the splanchnic nerve series into the lumbar region. The synapses are situated in the inferior mesenteric ganglion for the colon and in the hypogastric plexus and its subdivisions for the other pelvic organs The inferior mesenteric ganglion consists of an aggregation of ganglion cells in the aortic plexus immediately below the origin of the inferior mesenteric artery In man it is not always possible to define the ganglion clearly and the ganglion cells from which the postganglionic fibers for the pelvic viscera arise are widely distributed along the course

The fibers destined for the visceral structures contained in the orbit, such as the dilator pupillae muscle, Muller's muscle and the lacrimal glands, immediately join the internal carotid artery, which passes very near the superior cervical ganglion, and simply follow this artery and its ophthalmic branch to their destinations (Figure 31) In cases of severe facial paralysis, in order to enable a patient to close his eye, Leriche (1926) advocated removal of the tonic innervation of the smooth muscle of the upper lid by superior cervical ganglionectomy, thereby producing ptosis and enophthalmos

The fibers for the face (including the nasal mucous membranes) and for the salivary glands pass from the ganglion downward a short distance to join the external carotid artery, and follow the branches of the latter in their distribution According to the general rule that fibers supplying splanchnic regions follow blood vessels while those for somatic regions tend to follow the somatic nerve paths, the sympathetic innervation of the facial region would seem to characterize the latter as "visceral" in nature In a sense the face may be regarded as a "visceral" structure in that it is intimately associated with the oral portions of the respiratory and digestive systems, and, moreover, is itself the organ of expression

The postganglionic fibers for the skin of the head and neck (apart from the face region) join the roots of the cervical plexus (C-1 to C-4) and accompany the branches of the plexus to the periphery This is in accord with the general rule that sympathetic fibers supplying somatic regions reach their destination by way of the spinal nerves which supply that region, rather than by following the course of blood vessels or an independent course Some fibers from the superior cervical ganglion join the phrenic nerve

Sympathetic Innervation of the Upper Extremities· The preganglionic fibers for the upper limb arise in the lateral horn of T-2 to T-8 and occasionally from T-1, as well The axones of these neurones ascend in the sympathetic trunk and synapse in the inferior cervical and first thoracic ganglion with a few synapses in the second and third thoracic The postganglionic fibers, therefore, arise for the most part in the stellate ganglion and all join the roots of the brachial plexus and in this way are distributed with the branches of the plexus throughout the upper extremity

Sympathetic Innervation of the Thorax The intrathoracic viscera receive their sympathetic nerve supply from some of the upper thoracic segments (T-3 to T-7) Most of the fibers ascend in the sympathetic trunk, which carries them to the three cervical sympathetic

THE CRANIOSACRAL OUTFLOW (PARASYMPATHETIC)

The Cranial Outflow The cranial autonomic outflow is confined to certain of the cranial nerves, four in number (N III, VII, IX and X) The cranial autonomic fibers supplement the sacral outflow in that they supply parasympathetic innervation to all the splanchnic structures not supplied by the sacral outflow, namely those of the head, neck, thorax and extrapelvic portion of the abdomen The arrangement of the cranial outflow may be conveniently outlined by considering in order, from above downward, the visceral structures which must be provided with parasympathetic innervation

In the head there are four "visceral" regions which it is desirable to consider as quite separate for present purposes These are the orbit, the nose and throat region, the front of the mouth and the back of the mouth

In the orbit the structures which require a parasympathetic supply are the lacrimal gland and certain intrinsic smooth muscles of the eye, namely the sphincter pupillae and the ciliary muscle It would be agreeably simple and easy to remember if the arrangement of the parasympathetic supply were the same for all these visceral structures of the orbital cavity This is not the case, however Nature apparently aims to have the supply to the eyeball itself separate and distinct, for the preganglionic fibers for the intrinsic eye muscles mentioned emerge from the brain in the oculomotor nerve (N III), whereas those for the lacrimal gland emerge with the facial nerve (N VII) The former fibers (N III) end in the ciliary ganglion which is situated in the back part of the orbit and is the place of synapse The postganglionic fibers pass from this ganglion to the effector organs (sphincter pupillae and ciliary muscles) by way of the short ciliary nerves (Figure 31) The lacrimal gland s supply of parasympathetic fibers is similar to that of the nasopharyngeal region about to be described

The nasal cavity palate and pharynx require parasympathetic innervation for the numerous glands contained in the mucous membranes of these regions Moreover, these parts have to be capable of unusually efficient vasomotor responses because they are exposed to very direct contact with the external environment Hence the influence of the sympathetic vasomotor mechanism in this general region is supplemented by a considerable degree of parasympathetic control of the blood vessels The parasympathetic fibers for the region (and for the lacrimal gland) all emerge from the brain in the intermediate nerve, a part of the facial nerve (N VII) The synapses are congregated to-

of the hypogastric plexuses and are to be found as low down as the lateral aspect of the rectum

The postganglionic fibers reach their destination in the pelvic organs partly by following the blood vessels which supply the latter (e g , via the inferior mesenteric artery to the colon) and partly by an independent course, namely by way of the hypogastric plexus and its two subsidiaries, the pelvic plexuses The hypogastric plexus, which conveys the sympathetic fibers to the pelvic organs in both sexes, has been misnamed the "presacral nerve" It is prelumbar rather than presacral and it is a plexus rather than a nerve In 50 dissections Elaut found an intricate network of nerve fibers in 38 cases and a single nerve in only 12 cases Labate gives an excellent account of the surgical anatomy of the hypogastric plexus, based on dissection of 75 cadavers

The sympathetic nerve supply of the abdominal wall arises from the thoracic and lumbar segments of the spinal cord down to and including the second lumbar, which is the lower limit of any sympathetic outflow The fibers on leaving the spinal cord enter the nearby sympathetic chain ganglia, in which they terminate by synapse with postganglionic cells The fibers of the latter, in general, immediately join the spinal nerve trunks supplying the corresponding segments and are distributed with them to the abdominal wall The lumbar segments below the second lumbar receive some of the fibers by way of the sympathetic trunk

Sympathetic Innervation of the Lower Extremities It is in this same manner that the lower extremities are supplied with sympathetic fibers The lumbar and sacral somatic nerves which supply these extremities (L-2 to S-5) are obviously mostly below the lower limit of sympathetic outflow and therefore do not obtain any sympathetic elements directly from the spinal cord (excepting the L-2 nerve) There is, however, a chain ganglion corresponding to each of these nerves and the sympathetic component of the nerve is derived from this ganglion, all the necessary preganglionic fibers originate in and above the second lumbar segment (T-10 or T-12 to L-2) and descend in the sympathetic trunk to terminate in the chain ganglia (L-2 to S-5) below that level The postganglionic fibers, after passing from these ganglia to the lumbar and sacral nerves, are distributed by way of the lumbosacral plexus throughout the lower limb

Since the grey rami communicantes serve the purpose of conveying sympathetic impulses from the sympathetic trunk to the spinal somatic nerves, it is apparent that they are concerned only with somatic regions of the body, for example the blood vessels and sweat glands situated in the body wall and the extremities The grey rami do not carry any impulses destined for the thoracic or abdominal viscera

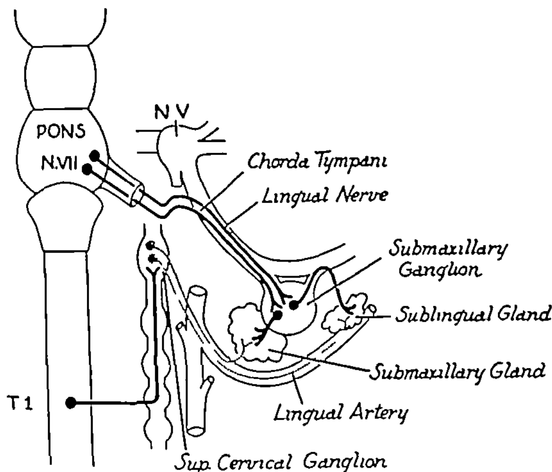


FIG. 33 Autonomic innervation of the submaxillary and sublingual glands. The submaxillary ganglion. (From Gray's *Anatomy* 23rd Edition Courtesy of Lea & Febiger Publishers.)

In the forepart of the mouth a parasympathetic supply is needed for the submaxillary and sublingual salivary glands and for the mucosa of the anterior two-thirds of the tongue The submaxillary gland, though situated somewhat posteriorly, may be considered related functionally to the anterior portion of the mouth inasmuch as its duct opens into that region The parotid gland for a similar reason is related to the posterior part of the mouth with respect to its innervation The preganglionic fibers for the anterior two-thirds of the tongue and the two anterior salivary glands emerge from the brain in the intermediate part of the facial nerve (N VII) The cells of the facial nucleus from which they arise are distinguishable from the rest of the nucleus and are designated as the superior salivary nucleus in contradistinction to another similar group of cells (the inferior salivary nucleus) situated a little lower down in the brain stem in relation to the nucleus of the ninth nerve, and functionally connected with the parotid gland The salivary and anterior tongue fibers contained in the facial nerve (N VII) soon

gether in the single sphenopalatine ganglion The preganglionic fibers reach this ganglion by way of the greater superficial petrosal nerve This nerve, like the chorda tympani, the tympanic and lesser superficial petrosal nerves, is an independent autonomic pathway quite analogous to the splanchnic nerves They are all merely short-cuts from the cerebrospinal nerves in which the autonomic fibers emerge from the central nervous system to a ganglion in which synapse must occur if the fibers are to accomplish their purpose of innervating smooth muscle or gland

The postganglionic fibers whose cell bodies are in the sphenopalatine ganglion, are conveniently distributed to the regions of the nose, palate and pharynx and to the lacrimal gland, by joining the various branches of the nearby maxillary division of the fifth nerve For the latter is distributed to these same regions supplying them with sensory innervation (Figure 32)

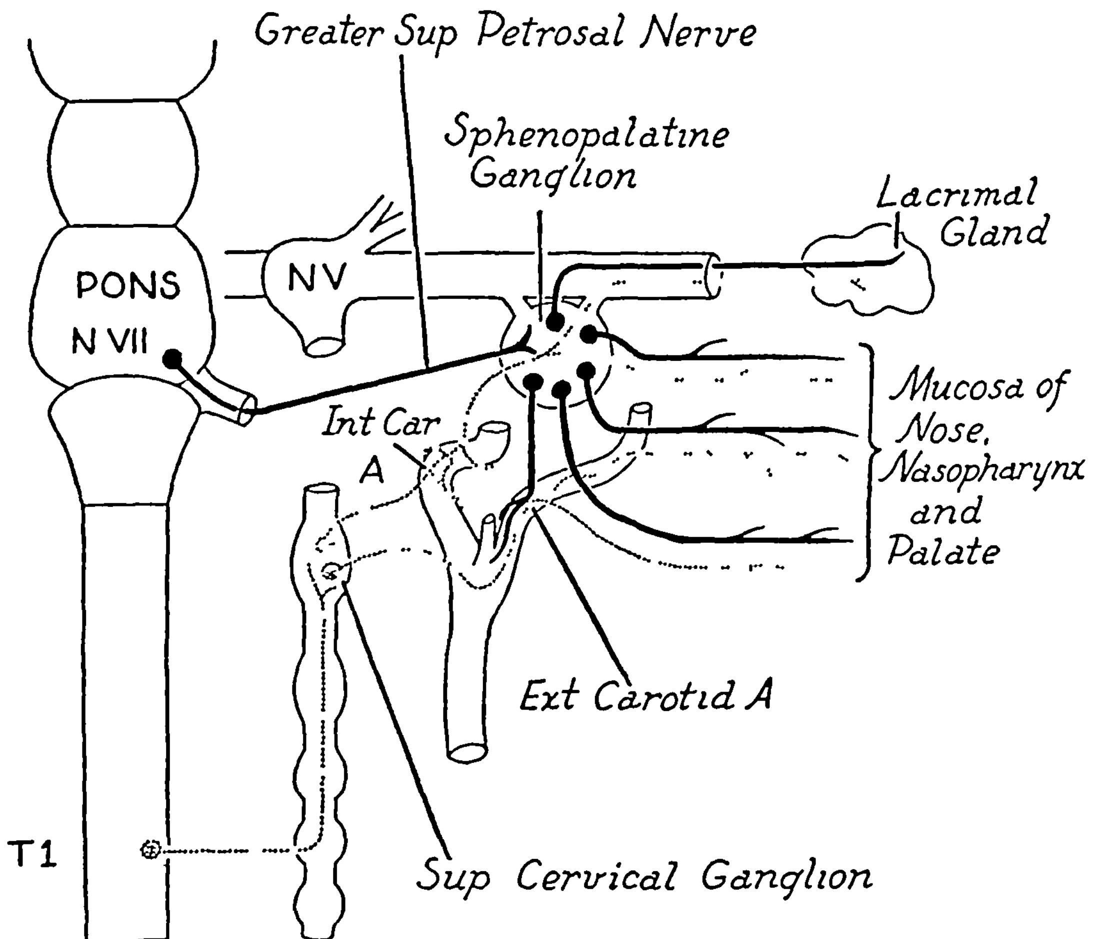


FIG 32 Autonomic innervation of the nasopharyngeal region The sphenopalatine ganglion (From Gray's *Anatomy*, 23rd Edition Courtesy of Lea & Febiger, Publishers)

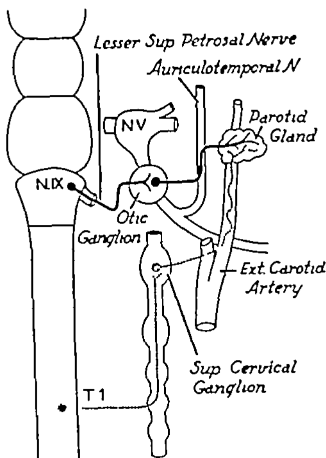


FIG 34 Autonomic innervation of the parotid gland. The otic ganglion (From Gray's *Anatomy* 23rd Edition. Courtesy of Lea & Febiger Publishers.)

ganglionic fibers are therefore generally longer in the parasympathetic than in the sympathetic system

The vagus supplies the heart, on which its influence is inhibitory It supplies the lungs with efferent fibers whose function is to bring about constriction of the bronchial tubes It supplies motor fibers to the entire digestive tract (including the bile passages) down to the hepatic flexure of the colon, and secretory fibers to the digestive glands including the liver, the pancreas and the gastric and intestinal glands The postganglionic fibers are for the most part quite short, since they are situated either entirely within the effector organs themselves or have their cell bodies in plexuses close to these organs The myenteric plexus of the alimentary canal is not composed of the postganglionic fibers of the vagus, but is thought to be an independent nerve network distinct from the pre and postganglionic elements of the vagus, but functionally influenced by the latter In this respect it is analogous to the specialized conducting system in the heart (the S-A node A V node and A V bundle) which does not take the place of the postganglionic fibers of

separate from the latter and for a time pursue an independent course as the chorda tympani toward their site of synapse, namely the submaxillary ganglion In the latter part of their course toward the ganglion they accompany the lingual branch of the trigeminal nerve (N V) as a matter of convenience, simply because the lingual nerve happens to run toward their destination As the lingual nerve passes near the submaxillary ganglion the parasympathetic fibers leave it and enter the ganglion, in which they terminate by synapse The postganglionic fibers for the submaxillary gland proceed from the ganglion directly into the gland which is contiguous with it The postganglionic fibers for the sublingual gland and for the tongue conveniently reach their destination by returning from the ganglion to the lingual nerve and accompanying it peripherally (Figure 33)

The parotid gland and the posterior one-third of the tongue derive their parasympathetic supply from the inferior salivary nucleus of the glossopharyngeal nerve (N IX) mentioned above In order to reach their point of synapse, the otic ganglion, the fibers leave the glossopharyngeal nerve near its root and proceed independently, first as the tympanic and then as the lesser superficial petrosal nerve Fibers of the postganglionic cells situated in the ganglion find a convenient route from the otic ganglion to the parotid gland by accompanying the auriculotemporal branch of the fifth nerve which happens to pass near the ganglion Other fibers reach the posterior one-third of the tongue by accompanying sensory branches of the glossopharyngeal nerve destined for that region (Figure 34)

The parasympathetic supply for the remaining viscera of the body down to the region innervated by the sacral outflow described later is conveyed entirely by the vagus nerve (N X) It is true that the spinal accessory nerve (N XI) at its origin from the brain contains some parasympathetic fibers, but all of these promptly leave the nerve and join the vagus trunk They may be considered vagus fibers, therefore, which merely happen to emerge from the brain with the spinal accessory nerve The autonomic fibers of the vagus have to have a synapse, just as do all other autonomic fibers However, the synapses of the vagus, unlike those of the rest of the cranial outflow just described, are not congregated in discrete ganglia, but are scattered about in nerve plexuses situated near the peripheral organs, and in some cases in the walls of the organs themselves This is in accord with the general rule that parasympathetic synapses and ganglia are situated rather peripherally, near the effector organs, in contrast to the sympathetic ganglia which are in most instances nearer to the central nervous system Pre-

the sacral autonomic fibers have no synaptic relation with the sympathetic trunks or with any somatic nerve trunks

Contrast between Sympathetic and Parasympathetic Divisions It will be noted that the parasympathetic subdivisions of the autonomic system supply in general only splanchnic regions, for anatomically they are not distributed to any portion of the purely somatic regions such as the thoracic and abdominal parietes and the extremities The sympathetic division on the contrary is distributed to all regions of the body, both splanchnic and somatic It is apparent, therefore, that in the somatic territory the sympathetic fibers must in some way subserve both motor and inhibitory functions with regard to glands and smooth muscle, since they are not counterbalanced there by any parasympathetic influence The chief purpose of the sympathetic innervation in somatic regions is to control blood vessels, sweat glands and erector pili muscles, both motor and inhibitory control of each of these functions resides in the sympathetic system There are no pathways by which fibers belonging to either the cranial or sacral outflow may reach the blood vessels of the extremities or the somatic portion of the trunk. The same is true with regard to the sweat glands and erector pili muscles in these regions Parasympathetic control over blood vessels is practically confined to the production of vasodilatation in the mucous membranes of the upper respiratory passages, in the salivary glands and in the generative organs

So much emphasis has been placed upon the balanced opposition between the two divisions of the autonomic system that an erroneous notion is prevalent that all organs which are innervated through the sympathetic division must also receive parasympathetic fibers and vice versa That this is not the case is clear from the fact that the parasympathetic supply is restricted to certain parts of the body, as described above, whereas sympathetic fibers are distributed everywhere Moreover, the idea of "functional antagonism" has been mistakenly expanded to signify that the sympathetic and parasympathetic nerves supplying a given organ always have exactly opposite effects, and that each division furnishes only excitatory or only inhibitory fibers for that organ There are numerous exceptions to the general rule of functional antagonism For instance, both the sympathetic and parasympathetic supply to the salivary glands are excitatory in that both induce secretion of saliva It is true that their effects differ in that one causes a profuse flow of watery saliva, whereas the other causes secretion of only a small amount of thick, tenacious saliva, however, this differ

the vagus, but is distinct from these though subject to their influence

The Sacral Outflow· The sacral outflow arises from the second and third (and often also the fourth) sacral segments of the spinal cord The fibers from these segments unite to form the pelvic nerve, which is often a plexiform structure rather than a unified nerve trunk These sacral preganglionic fibers pass uninterruptedly to the vicinity of the various pelvic organs which they supply Since the fibers arise from a rather restricted region of the cord and have to supply a quite extensive and complicated visceral area, they necessarily diverge widely from each other and pursue tortuous courses in order to reach all portions of the structures which require their controlling influence

Wherever a number of fibers happen to pass near or across others and mingle together more or less intimately for part of their course, the resultant latticework arrangement is described as a plexus, though the exact limits of the plexuses are generally not clear cut The pelvic nerve plexuses have no separate functional significance, since they are simply a convenient anatomical device for the distribution of nerve fibers It is true that the plexuses contain a certain number of synapses between the ends of preganglionic fibers and the cell bodies of the postganglionic fibers, but these synapses may be looked upon as situated within the viscera themselves, since the plexuses are for the most part in very close contact with the viscera supplied The postganglionic fibers, therefore, are situated almost entirely within the substance of the pelvic organs themselves

Functions of the Sacral Outflow: The sacral autonomic supply is motor to (stimulates) the large bowel below the level of the hepatic flexure, to the urinary bladder and to the muscle fibers about the prostate gland It is inhibitory to the sphincters of the bowel and bladder, and to the blood vessels of the external genitals Because of the latter function, the pelvic nerve is known as the nervus erigens in animals It will be noted that the sacral autonomic outflow has both motor and inhibitory functions, yet on consideration of each of its effects it will be apparent that it promotes several visceral activities in one direction in a coordinated manner, and that there is no real antagonism of function Thus, the motivation of the hollow viscera (colon and bladder) is harmoniously coupled with inhibition of the corresponding sphincters, the stimulation of the prostatic or uterine muscle fibers is associated with inhibition (i e, dilatation) of the blood vessels of the external genitals The generic function of the sacral outflow, therefore, is to promote nutritive and reproductive processes It should be noted that

adrenalin occurs only after seven or eight days, that is after degeneration of the vasomotor nerves

In direct opposition to these findings of Smithwick *et al*, are the findings of Fatherree, *et al*, in similar studies in Raynaud's disease of the hands The latter authors observed that increased sensitivity of the digital arterioles to adrenalin occurred in about the same degree after both preganglionic and postganglionic sympathectomy They do not believe that the unsatisfactory results in cases of upper extremity Raynaud's disease are adequately explained by the adrenalin effect on the digital arteriols

Simmons and Sheehan point out that whereas the hypersensitivity is maximal eight to 10 days after operation, it then decreases and by the time clinical relapse becomes apparent it may be absent These authors suggest that when relapse occurs early (within a few days) it may be due to some severe local fault in the digital vessels, and when relapse occurs late (after several months) it is probably due to regeneration of the vasoconstrictor nerve fibers or perhaps to a progressive fault in the vessels

Sensitization of the arteriolar musculature to the vasoconstrictor drug neosynephrine hydrochloride following peripheral nerve section has been demonstrated by Atlas by means of surface temperature measurements He suggests that the so-called trophic changes (vasomotor and nutritional) which occur in denervated tissues are the result of such sensitization to circulating vasoconstrictor substances McCloskey, *et al* had shown previously that after sympathetic denervation the action of adrenalin upon the peripheral vessels may become so intense as to produce necrosis of the skin when small amounts of the drug are injected subcutaneously, and that low environmental temperatures promote this necrotizing action

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"muscarine" effects are stimulation of gastric and intestinal peristalsis, inhibition of the heart and dilatation of blood vessels, with a resultant lowering of the blood pressure All these effects can be prevented or abolished by atropine

These facts suggest that all sympathetic and parasympathetic nerves are in a sense "secretory" nerves The function of the "chemical transmitters" which they produce is to distribute the autonomic impulses to a large number of smooth muscle cells There is evidence that only one smooth muscle cell in about a hundred receives a nerve ending These chemical mediators render an individual nerve supply for each contractile element unnecessary

The sympathetic substance (adrenalin) secreted at one point in the body may be carried by the blood stream to distant parts, thus producing a widespread effect The parasympathetic substance (acetylcholine) spreads to neighboring cells, but it produces a more localized response than the sympathetic substance because it is very unstable and is rapidly destroyed in the body by a specific enzyme, choline esterase Eserine, which is said to "stimulate" parasympathetic nerves, in reality augments their action by interfering with choline esterase and thus preserving the acetylcholine formed Atropine, which is said to "paralyze" parasympathetic nerve endings, acts by preventing access of acetylcholine to the effector cells After denervation, visceral structures become more susceptible to the action of adrenalin and acetylcholine Even skeletal muscle, when denervated, can be caused to contract by acetylcholine

Sensitivity to Adenalin Following Sympathectomy When sympathetic denervation is accomplished by dividing only the preganglionic nerve fibers, the postganglionic neurons do not degenerate and the sensitiveness of the effector organs to adrenalin and sympathin which results is only moderate in degree When the postganglionic fibers are divided, the resultant sensitiveness is much more marked

Ascroft states that after "preganglionic" sympathectomy the smooth muscle of the arterial walls becomes three times more sensitive than normally to circulating adrenalin and sympathin, whereas after "postganglionic" sympathectomy (when fiber degeneration is complete) the sensitiveness increases tenfold This rise of sensitiveness in the case of operations on the postganglionic fibers has been thought to be great enough to be a clinical handicap Smithwick *et al*, have pointed it out as one cause of failure of sympathetic ganglionectomy performed for Reynaud's disease They found that the increase in sensitiveness to

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